

THE EXPERIMENTAL PRODUCTION  
OF  
ADENOMYOMATOUS TUMOURS

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HISTORICAL SURVEY

No problem in gynaecology has excited greater interest and discussion during recent years than that which has centred around that widely diverse group of tumours collectively known as "The Adenomyomata". Some forty years have elapsed since their recognition as a definite pathological entity during which time many theories as to their mode of origin have been advanced, each one having resulted in a storm of pathological controversy. Though a lull has followed upon the most recent of these disputations - that initiated by Sampson, unanimity of opinion is by no means attained. Any contribution to the subject of Adenomyomata would be incomplete without reference to the varied phases through which opinion has passed, but as my work deals almost exclusively with animal experiments, and is of necessity only applicable to certain sub-divisions in this group of neoplasms, only a brief historical survey will be given before proceeding to outline the various phases of the work and the results achieved.

The term "Adenomyoma" refers to a tumour composed of gland tubules surrounded by a variable amount of embryonic connective tissue supported by smooth muscle. These elements are found normally

in the Uterus, the two former in the endometrium and the latter in the uterine wall but with strict definition between endometrium and myometrium. In adenomyomata this definition is lost and the gland elements are to be found not adjacent to the muscle layers but invading them by a non malignant permeation. Such tumours are practically confined to the female pelvic organs and may be either uterine or extra uterine, either of which varieties may take the form of a nodular tumour or a diffuse and widespread infiltration.

To Von Recklinghausen<sup>(1)</sup> must be given the credit of the first detailed description and classification of these tumours. In 1896 his very exhaustive treatise appeared with a detailed description of two classes of tumour - those arising from the cavity of the Uterus and those originating in the periphery. The former, he considered, arose through permeation of the uterine wall by the endometrium, and the latter, on account of their position and histological structure, he considered arose from meso nephric elements and consequently were of Wolffian origin.

In the same year that Von Recklinghausen published his work Cullen<sup>(2)</sup> produced an equally

important contribution to the subject in which he drew attention to the possibility of demonstrating in many of these tumours a direct spread from the uterine endometrium and he emphasized the importance of attributing to these growths a Mullerian origin. Both Cullen and Von Recklinghausen were probably correct as regards their description of the tumours, but whereas Von Recklinghausen had only seen a few of the centrally placed type and many of the peripheral, Cullen had only met with the former, hence Von Recklinghausen's leaning towards a Wolffian origin and Cullen's insistence on a Mullerian.

In 1900 another phase was entered upon by the publication of the work of Von Franqué<sup>(3)</sup> on "Salpingitis Isthmica Nodosa" in which he traced in many cases an origin of the epithelial elements in the tumours to the mucosal lining of the Fallopian tubes. In many of his cases there was recognisable an associated tuberculous infection of the adnexae and he postulated as a cause of the condition an outward migration of tubal epithelium as the result of chronic inflammation.

In the meantime, in 1898, another theory had been set afoot by Ivanoff,<sup>(4)</sup> namely, the "Serosal Theory". He maintained that cystic spaces in



peripheral adenomyomata arose from downgrowths of the peritoneum covering the surface of the Uterus and Fallopian tubes. R. Meyer,<sup>(5)</sup> stimulated by the work of Ivanoff and Von Franqué, made an exhaustive study of the possibility of an inflammatory genesis for these tumours and his conclusions supported both theories. He considered that uterine and tubal adenomyomata resulted from hyperplasia and metaplasia of the mucosal lining of the Uterus and tubes as the result of chronic inflammation and that diffuse adenomyoma of the recto vaginal septum was downgrowing of the peritoneum acting under a similar inflammatory stimulus. Thus we find at this stage four hypotheses, the Wolffian theory of Von Recklinghausen, the Mucosal theory of Cullen, the inflammatory theory of Von Franqué - also Mucosal, and the Serosal theory of Ivanoff.

Though during the next ten years a great deal of literature appeared on the subject and many cases were reported, no great addition to our knowledge was made until 1908 when Cullen's exhaustive work "Adenomyomata of the Uterus" <sup>(6)</sup> was published. He still maintained a mucosal origin for all uterine and extra uterine varieties and in everyone of the fifty cases he reported he had been able to trace

the continuity of the epithelial islets with the uterine endometrium. He considered that the starting point was in all cases a submucous myoma which became invaded by the endometrium. This, he considered, might remain stationary, become intra mural or even sub peritoneal and in this way he accounted for many extra uterine forms of the tumour. As far as I have been able to trace he was the first to report the presence of menstrual blood and the phenomenon of the menstrual cycle in these aberrant endometrial islets.

So far we have dealt mainly with uterine adenomyomata but a vast amount has also been written on the many extra uterine forms of the tumour. It is not my intention to dwell on these in any exhaustive manner except in regard to one type - that of the recto vaginal septum - so a passing reference is all I shall attempt. They have been described in the round, ovarian and broad ligaments, in the Fallopian tubes, recto vaginal septum and in the abdominal wall.

As we have already seen, those forms found in the Fallopian tubes were shown by Von Franqué to be an end result of a chronic inflammatory process and so were named by him collectively "Salpingitis Isthmica Nodosa", a view which Lockyer<sup>(7)</sup> supported

in his very comprehensive work "Fibroids and Allied Tumours".

Many adenomyomata of the broad ligaments have also been described and are so inter-related to the other varieties that a separate historical survey is impossible. They have, however, some unique features, for in the broad ligaments are to be found the Epoophoron and the remnants of Gaertner's duct, which led Joselin de Jong and Semmelink<sup>(8)</sup> to attribute a Wolffian origin to their classical case. Leitch<sup>(9)</sup> who in 1914 described a case of the nodular type assumed a pre-existing nodular tumour in the broad ligament which, he suggested, was a nodular parametritis, into which epithelium from the Cervix had migrated, and he was of opinion that the initial stimulus initiating the migration was of an inflammatory nature.

Adenomyomata of the recto vaginal septum are now recognised as being exceedingly common and within recent years, as the result of a revival of interests in this form of tumour, hundreds of cases have been recorded. According to Lockyer<sup>(7)</sup> one of the earliest recorded cases was that of Firth who removed the Uterus and a hard mass in the recto-vaginal septum by Wertheim's method under the impression that it was malignant, an impression that

led many of the earliest workers to undertake unnecessarily heroic operations. He considered the growth to be a relic of Muller's Duct. In 1909 R. Meyer<sup>(10)</sup> published five somewhat similar cases which he described as "para metritis nodosa posterior" attributing to all an inflammatory origin, while Leitch<sup>(9)</sup> in 1914 described two of these growths as submucous nodules which had been pushed backwards into the recto vaginal septum and had thus lost continuity with the uterine cavity. He emphasized their Mullerian origin from the uterine cavity rather than from embryonic rests.

In 1918 appeared Lockyer's magnificent work on the subject "Fibroids and Allied Tumours" and no review would be complete without a summary of the various opinions expressed by him and some analysis of his final conclusions. His first open expression of opinion is in reference to "Salpingitis Isthmica Nodosa" which, like Von Franque, he considers to be a late manifestation of an inflammatory tubal condition. In regard to the extra uterine forms of adenomyomata, particularly those associated with the upper part of the genital tract, such as round ligament tumour, he entirely disagrees with Cullen and does not consider them to arise from the uterine mucous membrane by a



process of migration but considers them to be of mesonephric origin for topographical rather than morphological reasons.

In his discussion on adenomyomata of the broad ligament he supports Leitch's view of a "migratory adenoma" but supplements it by suggesting an inflammatory genesis from either the Cervix below or the uterine cornua above. He points out that epithelial hypertrophy is particularly common in the Cervix owing to its liability to laceration and "erosion", and in the uterine cornua as the result of salpingitis.

"The sites of election within the broad ligaments will obviously be at the top and the bottom, that is, in the meso salpinx where we have growths arising from salpingitis and also from the Epoophoron, also in the cellular tissue around Mackendrodt's cervical ligaments where parametritis with epithelial hypertrophy is liable to occur".

In regard to recto vaginal adenomyomata he will not admit of an origin from the uterine mucosa, but favours the view that either the peritoneum, vaginal epithelium or Mullerian relics supply the glandular inclusions, a view which is a little difficult to reconcile with his explanation of an inflammatory cause for the broad ligament varieties.



In reviewing all the work up till 1918 we find no real unanimity of opinion amid all these conflicting views and the four theories - Mucosal, Wolffian, Serosal and that of embryonic rests all have their firm supporters, some maintaining an inflammatory genius and some a purely neoplastic one. The reason for this has possibly been a failure to realise a diversity of types of the "tumour" and the consequent improbability of explaining all by one hypothesis led to much confusion. For example a solitary nodular extra uterine "tumour" can hardly be compared with that type which shows a widespread and diffuse infiltration, for the former may well be a dysembryoplasia and the latter a reaction in response to an unknown stimulus. Each theory is applicable to different types of adenomyomata, and it may not be unreasonable to assume that all parts of the pelvic viscera that have arisen from the genital ridge contain elements capable, under the action of certain stimuli, of producing tissue of an adenomyomatous type. •

The year 1921 marked a new epoch in the history of Adenomyomata for in June of that year John A. Sampson of Albany, New York, read before the American Gynaecological Society a paper on "Perforating Haemorrhagic Cysts of the Ovary" and demonstrated the association between this condition and pelvic adenomyomata.<sup>(11)</sup> He described fourteen cases occurring in women between the ages of thirty and fifty years, all of which were characterised by the presence of adherent ovarian cysts containing chocolate coloured fluid, and widespread adhesions between the posterior surface of the Uterus, broad ligaments and rectum. Pathological examination had revealed tissue of endometrial type lining the interior of these tarry cysts and also infiltrating the ovary, its ligaments and the pelvic adhesions. One of the most striking features of this adenomyomatous tissue was its ability to produce periodic haemorrhage analagous to menstruation. He concluded that these haemorrhagic cysts of the ovary contained tissue of endometrial type, that rupture of the cysts disseminated both menstrual blood and menstrual epithelium into the pelvic peritoneum and that these endometrial fragments were capable of implanting themselves on the pelvic peritoneum and viscera and there continuing

to grow.. He was of opinion that the widespread pelvic adhesions were due to the irritating action of the escaped menstrual blood and that the adenomyomatous infiltration of the posterior uterine wall and recto vaginal septum was due to an invasion from without by the epithelial islets implanted in the posterior cul de sac after rupture of the cysts. Though other workers had described and speculated on the origin of these cysts Sampson was undoubtedly the first to demonstrate a series of cases and to show that all were associated with a widespread adenomyomatous infiltration.

The following year<sup>(12)</sup> he went further and explained the origin of the tarry ovarian cysts as being due to implantation on the ovaries of endometrial fragments carried there from the uterine cavity by a process of retrograde menstruation through the fallopian tubes. The ovaries he thought acted as intermediate hosts in this process of endometrial dissemination, The first stage was the implantation of endometrial fragment on the ovaries with the consequent formation of ovarian haematomata, and subsequent rupture of these "tarry ovarian cysts" caused widespread dissemination of endometrial tissue throughout the pelvic cavity. Thus arose what

has come to be known as Sampson's Theory; from the practical standpoint it has brought about fairly widespread recognition and uniformity in the operative treatment of this condition, and for the pathologists it has provided the fillip necessary for a renewal of thorough pathological investigation in a field which for some years had been neglected.

Sampson's subsequent work has been largely a reiteration of his original views in an attempt to bring forward more conclusive evidence in support of his theory. It is unnecessary to quote all his many contributions but certain amplifications that he has made can justifiably be mentioned. Shortly after his original publications he described eight cases of adenoma of endometrial type involving portions of the alimentary tract - a type that had been described previously by many workers, <sup>(13)</sup> He adhered to his original explanation of dissemination by retrograde menstruation but for the first time he admitted the possibility of lymphatic endometrial spread by the pelvic lymph channels as an explanation of the occurrence of adenomyomata in these more distant sites. In 1925 he described seven cases of ovarian carcinoma whose origin he attributed to malignant change in pre-existing endometrial cysts in the ovary and whose



histological structure was similar to adenocarcinoma of the corpus uteri.<sup>(14)</sup> In 1927 he published two further cases<sup>(15)</sup> and<sup>(16)</sup> in which he demonstrated the possibility of a venous and lymphatic spread for endometrial emboli cast off from the mucosa lining the uterine cavity and also from ectopic endometrial foci during menstruation. Though accepting this alternative method of endometrial dissemination he still adhered to his original explanation by retrograde menstruation.

His most recent work has been an investigation of "endometriosis" following salpingectomy<sup>(17)</sup> and,<sup>(18)</sup> his theory having received somewhat of a setback by the publication by D. Dougal<sup>(19)</sup> of a case of tarry ovarian cysts found by him in a woman eleven years after bilateral salpingectomy. Sampson claims to have found endometrium in and about the tubal stumps in thirty out of thirty six patients on whom salpingectomy for various reasons had been previously performed. This he considers to have arisen from "sprouts" growing out from the traumatised mucosa of the tubal stump and which invade adjacent structures. He also described a case of tarry cysts developing after salpingectomy but considers that the aberrant endometrium was scattered at the first operation.



Such a far reaching assertion as Sampson's was bound to have its repercussion among many other observers and this historical survey would be incomplete without some reference to the more important views and criticisms that have been advanced following Sampson's re-opening of the subject. Donald of Manchester<sup>(20)</sup> had made a close study of the clinical aspect of these tarry ovarian cysts for some years before Sampson's pronouncement and had suggested to his pathologists the possibility of active endometrium being present in such ovaries, but unfortunately for him no such pathological confirmation was forthcoming. He is in complete agreement with Sampson and considers retrograde menstruation as being the most probable cause of their occurrence. Blair Bell<sup>(21)</sup> disagrees with the name adenomyoma and has suggested the terms "Endometrioma" and "Endometrio myoma" as being more truly descriptive of the tumours, terms which have received a fairly widespread acceptance. He does not accept Sampson's view but maintains that the cause of endometriomata is either an infiltrative process resulting from direct contact or a late result of the congenital aberration of coelomic epithelium, an accidental occurrence he describes as "Müllerian aberration". To quote "The

appearance of a functional structure such as endometrium in abnormal situations can only result from congenital aberration when not due to direct contact". Bailey<sup>(22)</sup> in an exhaustive microscopic study has confirmed Sampson's findings and claims to have demonstrated the various stages in the growth of ovarian and recto vaginal endometriomata from the initial phase of implantation to the maturer forms of the condition.

Perhaps the most exhaustive and comprehensive review of the subject in recent years was that of Lauche<sup>(23 & 24)</sup> who in 1923 and 1924 published two articles on his observations made subsequent to Sampson's pronouncement. Lauche sums up admirably in saying that nothing substantial can be brought against Sampson's view, but he is cautious in his acceptance and prefers to regard adenomyomata as being of six different types, each with its own mode of origin. The six types described by him are as follows:- Those resulting from a regenerative process, those resulting from hyperplasia and those from metaplasia. Some he considers result from actual transplantation of endometrial tissue, but some he thinks are dystopic in origin and a few possibly are of the nature of blastomata. He wisely refrains from accepting any one theory and covers himself by suggesting all!

In 1925 there appeared a detailed description of three cases of diffuse pelvic adenomyomata and a critical etiological review by Letulle, Tuffier and Lambert.<sup>(25)</sup> For an explanation they adopt Conheim's theory of foetal residues by which he explained the origin of tumours. Just as Conheim thought that such "rests" might develop into cancer and other neoplasms, so they consider that Mullerian and Wollfian residues may produce, under some unknown stimulus, endometriomata. They sum up by describing endometriomata as a formative aberration of the female genital organs and compare the condition with accessory pancreatic buds found at the entrance of the duodenum.

In the same year de Jong who, it will be <sup>(26)</sup> remembered, published his clinical case in 1903, again entered the lists and together with de Snoo described a case of a woman at term who developed obstructed labour owing to a soft tumour in the Pouch of Douglas. . Caesarean Section was performed and after delivery a tumour mass was felt in the posterior uterine wall and both broad ligaments. So, under the impression that it was sarcomatous, total extirpation was decided upon. Microscopic examination revealed a diffuse adenomyoma showing decidual change throughout the endometrial elements

and named by them "adenosis decidualis". For diffuse adenomyoma arising from the endometrium itself they suggest the fitting name "endometriosis" and for similar growths arising peripherally "endometrioma". They refuse to accept Sampson's theory but attribute these growths to the coelomic epithelium. "Part of the peritoneal tissue in direct continuity with the coelomic epithelium have kept attributes which, with regard to their function have the specific character of the female genital tract. It is not unintelligible that there can be cases when parts of the coelomic peritoneal epithelium have not only kept the attributes of the endometrial epithelium but the capability of furnishing perfect endometrium". They quote eleven cases in support of their contention, and one of the cases where adenomyoma of the small intestine was removed for obstruction and five years later a tarry ovarian cyst developed they consider directly contradicts Sampson's theory.

(27)  
According to Halban Sampson's theory is insufficient to account for many of the types of adenomyoma and he favours the view that a more probable origin is the dessimination of endometrial fragments by the lymphatic channels, a view that has been, to some extent, accepted by Sampson himself.

The subject was discussed fully at a meeting of the American Gynaecological Society in 1926.

(28)  
Novak, in discussing Sampson's opening paper disagreed entirely with his theory of retrograde menstruation and gave the following reasons for his decision:-

1. The endometrial like tissue sometimes found in the tubes at operation probably comes from endometrial like tissue in the ovary, for the fragments are too large to have regurgitated from the uterus.
2. That regurgitation of menstrual blood is very infrequent, as shown by operations.
3. That retrograde transportation of endometrium is very improbable as it would be against the ciliary current, against tubal peristalsis and moreover, the tubal lumen is too narrow.
4. That cast off endometrium is degenerating and probably could not live.

He concluded by stating there was as yet no evidence that implantation played any part whatever in the production of adenomyomata, and suggested the ectopic differentiation of coelomic epithelium as a source of aberrant endometrium. J. R. Goodall<sup>(29)</sup> at the same meeting, stated that after the examination



of 22000 ovarian sections he attributed the origin of endometriosis to ectopic embryonal tissue of an endometrial nature in the ovary.

Sampson's theory received a further setback by the publication in 1926 by D. Dougal<sup>(19)</sup> of a case of tarry ovarian cysts occurring many years after bilateral salpingectomy. Dougal suggested the following three possibilities:-

1. Endometrial tissue may have been in the ovaries before the tubes were removed.
2. One or both tubes may have been left patent after operation,
3. The endometrium may have extended directly from the uterine cavity to the ovary through intervening structures by a process of infiltration.

Dougal believed the latter explanation to be the correct one.

In 1924 W. W. King<sup>(30)</sup> reported having operated upon over one hundred cases of endometriomata and stated that he considered a pre-existing pathological condition in the uterus and appendages to have been present in practically every case. He found fibroids in 22%, adherent retroversion in 21% and

evidence of pelvic inflammation in 39.7%. He considers that some such pre-existing pathological condition is the starting point in all cases of endometriosis. Keene and Kimbrough<sup>(31)</sup> in an analysis of 118 cases came to a similar conclusion. They found that in intra peritoneal endometriosis complicating disease was a striking feature, fibroids being present in 55.4 % of cases, salpingitis in 20% and an adherent retroflexion in 14.5%. Thus we find that ten years after the first discovery, we are little, if any, nearer a solution to the mystery that surrounds the adenomyomata. To Sampson gynaecology owes a great debt for the brilliant execution of his pathological research and the careful formulation of his views have done much to advance our subject. Though his theory is not proved it has provided a stimulus for world wide investigation which still continues and may yet be productive of results which cannot at present be estimated.

The experimental work, which is the main aspect of this thesis, was undertaken primarily to investigate the behaviour of transplanted normal endometrium and to study its mode of growth under varied influences. No originality is claimed for the conception for, as will be seen later, other workers have explored this avenue, though prior to the first of these experiments only one investigator - Jacobson - had undertaken it in relation to the study of adenomyomata.

The earliest recorded work is that of  
(35)  
Stilling in 1910. Experimenting with rabbits he transplanted pieces of vagina, uterus and endometrium and embedded them in the spleen and was able to produce three cysts of varying size. These he found were lined with ciliated columnar epithelium, contained a clear fluid secretion under tension and yet showed papillary projections into the interior. By performing a second experiment on the same animal he found that the cyst regenerated after portions had been removed. Kerwin and  
(36)  
Loeb in 1918 transplanted pieces of the kidney, thyroid, uterus and endometrium of guinea pigs to the ear and abdominal wall of the same animals and observed the resultant growth at varying intervals.

Régeneration and persistence of growth was shown to a much greater degree in the case of the endometrium than with kidney or thyroid tissue. In 1922 Ebeling and Fischer<sup>(37)</sup> made experimental tissue cultures of uterine epithelium and demonstrated its ability to form a delicate continuous layer over the surface of the artificial medium. In the same year Jacobson<sup>(38 & 39)</sup> in an attempt to find some confirmation for Sampson's views on the aetiology of adenomyomata, implanted small pieces of rabbit endometrium into the peritoneal cavity of the same animal and was able to produce implantation endometrial cysts which he thought comparable to tarry ovarian cysts as found in the human female. Later<sup>(40)</sup> he repeated these experiments and made autogenous grafts in menstruating monkeys and produced cysts whose histological character, manner of development and reactions to the ovarian hormone favoured Sampson's theory of the origin of ectopic endometriosis in the human being.

More recently O'Keefe and Crossen<sup>(41)</sup> working on dogs have produced successful implantations in the region of the appendix and have demonstrated the tendency for such implants to cause dense adhesions in their vicinity. In 1927 Allen and Bauer<sup>(42)</sup> performed similar transplants into the anterior

chamber of the eye in rabbits in order that the behaviour of the grafts from day to day might be observed. The grafts "took" successfully in 88% of the twenty five cases when the implant was made in the eye, but in only 8% of grafts embedded in the abdominal wall. They found that the columnar epithelium rapidly proliferated and covered the anterior chambers but provoked no connective tissue reaction in the subjacent tissues, and that no proliferative tendency was shown by the stroma or muscle.

It will be seen that these workers confined their experiments to the study of the implantation of normal endometrium. There seemed to me a possibility of applying this conception not only to the study of ectopic endometrium and its bearing on Sampson's implantation theory, but also as a means of studying the other concepts, namely, the serosal and inflammatory theories on the genesis of adenomyomata. Moreover, it seemed not unlikely that even though negative results should be obtained it would be possible to make some observations on the behaviour of misplaced endometrium under the action of varying influences.

Some sixty experiments have been performed. A proportion of these have been merely confirmatory



and others have given negative results, so only those which have given positive results will be described in full detail. Many difficulties have been encountered, not the least being the microscopic preparations for the implants have often presented great difficulty in recognition owing to their minute size and to their being frequently buried in adhesions, so that in every case serial sections have been necessary in order to make certain that no portion should be missed. Unexpected deaths among the animals have necessitated repetition of much of the work and epidemics of disease to which rabbits are peculiarly liable have also been a source of delay. I am much indebted to Professor Raper, Professor of Physiology of the Victoria University of Manchester for his kindness in placing his department at my disposal for the carrying out of this experimental work.

OBSERVATIONS ON THE GROWTH OF SIMPLE  
AUTOGENOUS ENDOMETRIAL TRANSPLANTS

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EXPERIMENT NO. I.

Date:- February 1925.

Animal:- Half grown Angora Rabbit.

Technique:

Under Ether Anaesthesia the hair on the abdomen was cut very short and the abdominal wall painted thoroughly with tincture of iodine. The abdominal cavity was opened by a mid line incision exposing the uterine cornua, and the intestines were packed off by gauze soaked in saline. The left cornu of the uterus was resected between fine catgut ligatures, the lumen was opened up throughout the entire length and small pieces of endometrium were shaved off with a sharp scalpel. A stab wound was then made in the left ovary and a small piece of endometrium about 2 sq. M.M. in size was buried in the stab wound, which was then closed by a fine catgut stitch. A second piece of endometrium was then fixed to the peritoneum covering the anterior aspect of the pelvic colon by a fine catgut stitch. The abdominal wall was then closed by two layers of continuous catgut sutures - No. 000, 20 day iodised, with a layer of interrupted silk worm gut sutures for the skin.

The rabbit made an uninterrupted recovery from the operation but died of coccidiosis on the eighteenth day.

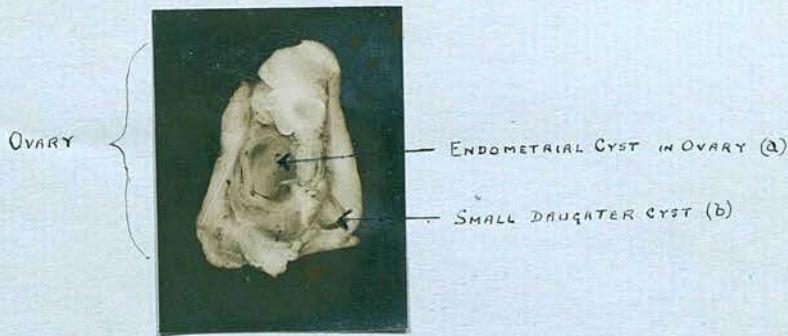
Post Mortem Examination:

On opening the abdomen no adhesions were found and all the abdominal viscera were perfectly healthy. There were no adhesions present where the left cornu had been resected and the stump was healthy and the lumen closed. Examination of the left ovary (Fig. I) revealed the presence in it of a dark bluish coloured cyst (a) where the endometrial grafts had been implanted and posteriorly the cyst had burrowed into the posterior abdominal wall. The ovary and part of the posterior abdominal wall, together with the cyst, were removed in one piece for examination. Firmly incorporated in the anterior wall of the pelvic colon was the second graft (Fig. IV) forming a pinkish nodule about the size of a pea (a) and considerably larger than the size of the original graft. In both cases the original catgut ligatures used to fix the grafts in position were present and in neither case were there any adhesions to adjoining viscera.



SPECIMENS.

Ovary. Macroscopic Examination: Fig. I:



The ovary was normal in its upper two thirds, but growing in the lower pole was a dark bluish coloured thin walled cyst (a) rather larger than the ovary - about 1 cm. long and .7 cm across, and firmly incorporated in the ovarian tissue.

Posteriorly the cyst was to some extent embedded in the posterior abdominal wall. On the anterior surface there was a small thin walled daughter cyst about the size of a pin head (b).



Microscopic Examination: Figs. II and III:

The specimen was fixed in alcohol and embedded in paraffin after being passed through chloroform. Serial sections were cut through the whole specimen and every fifth section was stained, mounted, and examined in order that no part should be missed.

Fig. II. Endometrial Graft in Ovary

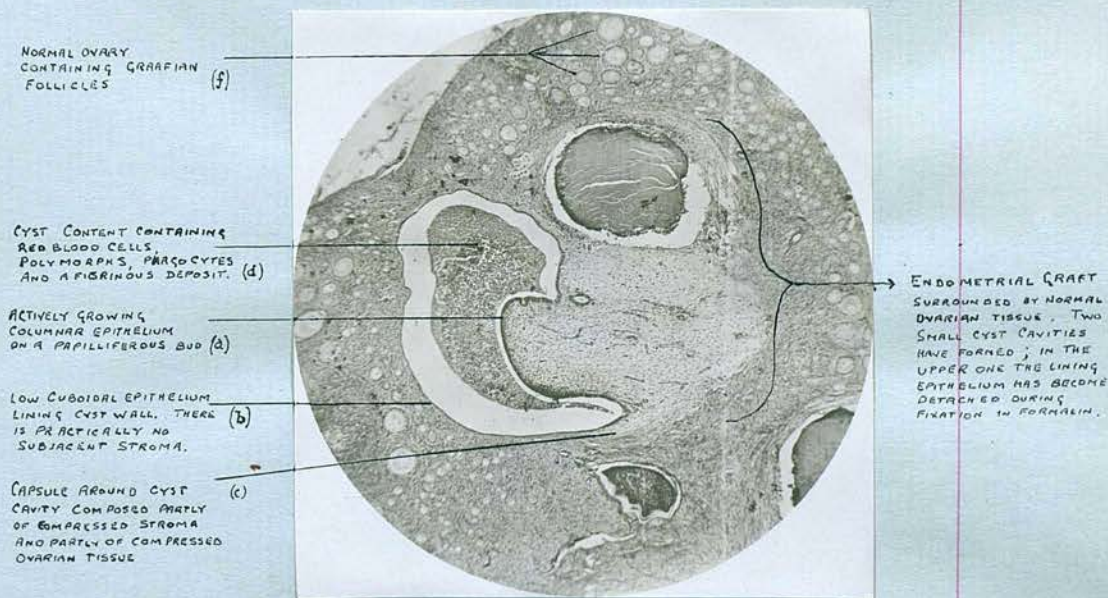
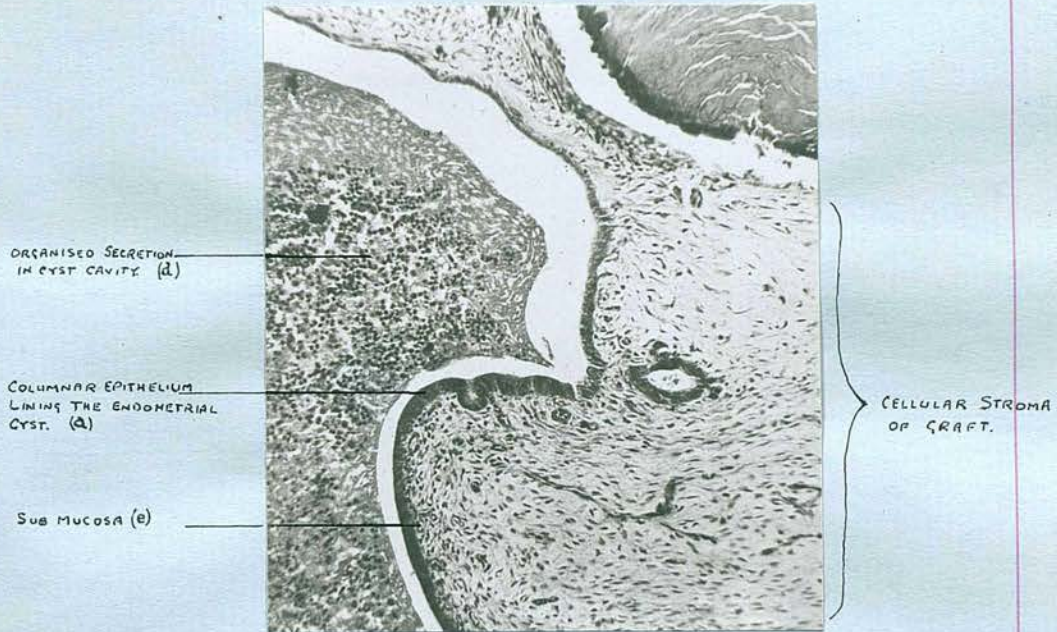




Fig. III.

Endometrial Graft in Ovary

High Power.



ON THE RIGHT CAN BE SEEN THE CELLULAR STROMA OF THE  
ENDOMETRIAL GRAFT. ON THE LEFT IS A PORTION OF THE  
CYST CAVITY LINED BY ACTIVE COLUMNAR EPITHELIUM (a)  
THIS CYST IN THE OVARY RESEMBLED A TARRY CYST  
AND THE CYST CONTENT IS SEEN TO CONTAIN RED BLOOD  
CELLS, POLYMORPHS, PHAGOCYtic CELLS AND FIBRIN. (d)  
BENEATH THE EPITHELIUM IS A LAYER OF COMPRESSED  
STROMA FORMING A SUB MUCOSA. (e)

In the ovary can be seen a multilocular cyst adenoma growing from the endometrial graft and which appears to have burrowed into the ovarian tissue by which it is now practically surrounded. The cyst cavities are lined by epithelium varying from the low cuboidal to the high columnar type in varying stages of cellular activity. The lining epithelium is most active on the papilliferous buds (a) where the subjacent stroma is most plentiful and cellular, in contrast to the lining cyst wall (b) where there is little stroma and the epithelium is of the low cuboidal type. The outer capsule of the cyst is thin and composed of compressed fibrous and muscular tissue, partly derived from the stroma of the endometrial graft and partly from the compressed ovarian tissue (c). There is no basement membrane and the nuclei are large and deeply placed, while here and there cilia can be made out. The stroma consists of loose reticular tissue containing many spindle cells, blood vessels and lymphatics, and here and there collections of round cells. Beneath the epithelium is a rather more compact layer forming a submucosa (d). In the cyst cavity can be seen a mass of fibrins containing red blood cells, polymorphs and phagocytic cells (e). Adjoining the cyst the ovarian tissue is perfectly normal and healthy, and many primordial follicles and corpora lutea are



present (f). It is interesting to note that there is no sign of any infiltration of the adjoining tissue by the endometrium and it appears to form a non invasive implantation cyst.

PELVIC COLON.

Macroscopic Examination Fig. IV:

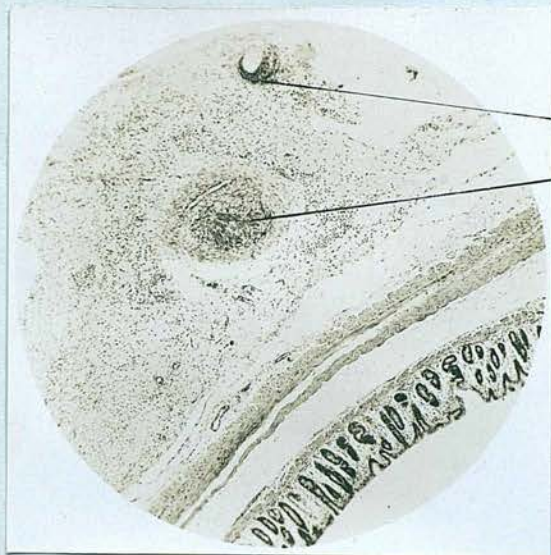


Firmly incorporated in the wall of the pelvic colon was the second graft forming a nodule about the size of a pea and pink in colour in contrast to the whiteness of the colon wall (a). At the junction of the graft and the wall of the colon numerous small blood vessels could be seen forming an adventitious blood supply, and the graft appeared to have become covered by peritoneum.



Microscopic Examination Figs V, VI and VII:

Fig. V. Endometrial Graft on Pelvic Colon



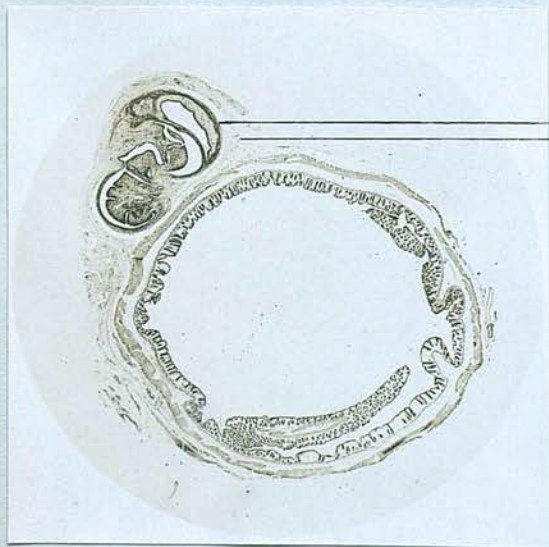
ISLETS OF ENDOMETRIUM  
GROWING ON  
WALL OF PELVIC COLON. (ad)

MUSCULAR LAYER OF PELVIC COLON.

MUCOSA OF PELVIC COLON.

NOTE THE INFILTRATION OF ROUND CELLS AND  
PHAGOCYtic CELLS AROUND THE ISLETS OF  
ENDOMETRIUM. ALSO THE COMMENCING  
GROWTH OF SMALL ADVENTITIOUS BLOOD VESSELS.  
THE ENDOMETRIAL STROMA HAS PERSISTED  
BUT THE COLUMNAR EPITHELIUM IS VERY  
ILL DEFINED.

Fig. VI. Endometrial Graft on Pelvic Colon.

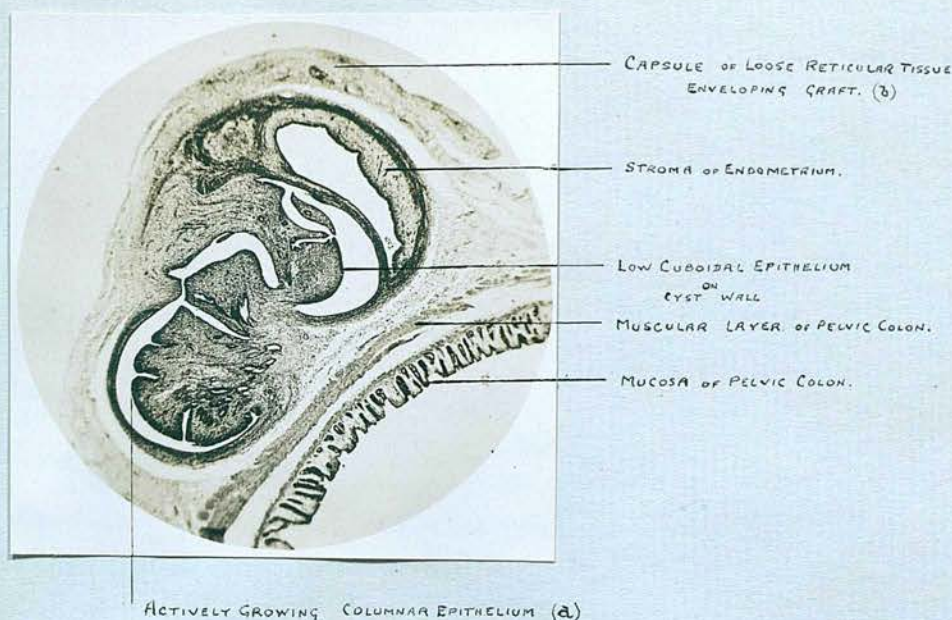


ENDOMETRIAL GRAFT FORMING CYST ADENOMA.  
SEROsAL LAYER GROWING OVER GRAFT  
AND FORMING CAPSULE (b)

PELVIC COLON



Fig. VII. Endometrial Graft on Pelvic Colon.  
High Power.



Serial sections of the graft on the peritoneal surface of the pelvic colon show that it also has formed a multilocular cyst adenoma. As in the case of the ovarian graft the lining of the cyst cavities varies from low cuboidal to high columnar epithelium and the cells have the same characteristics. Supporting the epithelium is a thick layer of stroma in varying stages of cellular activity, growth being most active in the papilliferous buds (Fig. VI (a)), the same being found in the case of the epithelium. Unlike the ovarian graft there is no exudate in the cyst cavities and none was found throughout the serial

sections. Completely enveloping the graft can be seen a capsule (Fig. VI (b) ) of very loose reticular tissue apparently developed from the sub serous layer of the wall of the pelvic colon over which is the serosal layer continuous with that of the colon. As in the ovarian graft there is no evidence of any invasive tendency, the muscular layers of the colon being intact.

Fig. VII shows the growing edge of the graft with two small islets of endometrium (aa) surrounded by a large area of loose connective tissue, fine blood vessels and lymphatics apparently developing from the sub serosa. Surrounding the islets of endometrium are large numbers of polymorphs but no phagocytic cells can be seen. It is remarkable that the graft should provoke such an extensive reaction in the sub serosa in view of the fact that the adjoining tissues apparently make little attempt to limit the growth of the foreign element in their midst.

This experiment has confirmed some part of Jacobson's work and has shown that pieces of endometrium when transplanted to the interior of the ovary or to the peritoneal surface of the

colon will continue to exhibit active growth, and that such growth tends to produce multilocular cyst adenomata.

It was considered that further experiments were necessary before this could be accepted as a certain fact, and it was decided to perform experiments in order to observe, step by step, the mode of growth of these endometrial grafts and the changes leading up to cyst production. With this in view it was decided to perform autogenous transplantation of endometrium in a series of rabbits and to examine them subsequently at intervals of three, six and nine days. If successful then growth over much longer periods could also be studied.



EXPERIMENT NO. II.

For this experiment an almost fully grown female rabbit of unknown species was used. The same technique as in Experiment No. I was adopted and care was taken that the field of operation should not be in any way contaminated by antiseptics, as it was thought that such contamination might in some unknown way influence the growth of the grafts. The right cornu of the uterus was resected, opened up along its entire length and the endometrium, which was rather thin and scanty, shaved off with a sharp scalpel. This was divided into eight pieces which were placed without any artificial fixation in various parts of the pelvic cavity. Three pieces were placed on the anterior surface of the left uterine cornu, two on the posterior pelvic wall, and three were scattered in the pelvic cavity. Three days later the animal was killed and a post mortem examination was made.

Post Mortem Examination:

On opening the peritoneal cavity there was little evidence of the previous operation and there were no adhesions. All eight pieces of endometrium were found fairly easily. Two were found on the anterior surface of the left mesosalpinx, two were adherent to the anterior abdominal wall close to the scar, a position to which they had presumably fallen when the rabbit resumed its normal posture, one was adherent to the posterior abdominal wall, one was lying free in the recto vaginal space, and two were adherent to the peritoneal surface of the pelvic colon. To one of the grafts on the pelvic colon a loop of small intestine had become adherent. It was noted that although seven of the eight grafts had become adherent to the structures mentioned and had apparently established themselves in this short time, yet there appeared to be no tendency, except in one case, for adjoining structures to become adherent to the graft.



Macroscopic Appearances:

All the grafts had become smoother and more rounded in appearance than when inserted and the original irregular shape had given place to a more rounded or oval outline. With the exception of the loose graft lying in the recto vaginal space they were deep red in colour and very congested, rather like small pieces of organised blood clot. They appeared to be rather larger in size than when they were inserted, and on the adjacent surfaces of the viscera to which they had become adherent numerous small blood vessels could be seen, due either to local irritation from the presence of the grafts, or to an attempt on the part of the adjoining tissues to form an adventitious blood supply for the new tissues. The loose graft was quite pale in colour, was also smooth in outline but had lost the glistening appearance of the original endometrium.

The changes that have taken place in the endometrial graft are rather striking and can be compared side by side with the endometrium in the normal uterus, the left uterine cornu having been left intact at the operation, as seen in the upper part of the section. (Fig. VIII-a) The deep red colour of the graft is explained by the presence of a large amount of blood pigment (b) in the stroma. Presumably there has been some disintegration of the fine vessels in the stroma with diapedesis of red corpuscles into the stroma itself. The subsequent breaking down of these red blood corpuscles accounts for the presence of the blood pigment. The normal glandular acini in the lining columnar epithelium have disappeared almost entirely, there are no tubular glands present and what columnar epithelium remains has changed to a low cuboidal type covering the outer surface of the graft. In the lower corner (Figs. VIII and IX - c) is an area of fairly normal and active endometrium showing a more typically glandular appearance, but here also the stroma shows engorgement with blood or blood pigment, though in

a lesser degree. The whole graft has become anchored to the mesosalpinx by a layer of fibrins of varying thickness. (Fig. IX - d)

A most interesting phenomenon - shown rather better in Fig. XIII can be seen in the connective tissue of the adjoining broad ligament. Here the connective tissue cells appear to have undergone a stroma like reaction, presumably as the result of some stimulus from the adjoining graft. (Fig. IX - e). The connective tissue cells have assumed an almost embryonic form, being irregular in shape, with branching protoplasmic processes, and the whole area has become highly cellular. This reaction would appear to be similar to the formation of the "cytogenous mantle" around the islet of epithelium seen in cases of diffuse adenomyoma of the uterine wall in the human female.



Microscopic Appearances:

Endometrial Graft on left mesosalpinx Figs.VIII & IX.

Fig. VIII

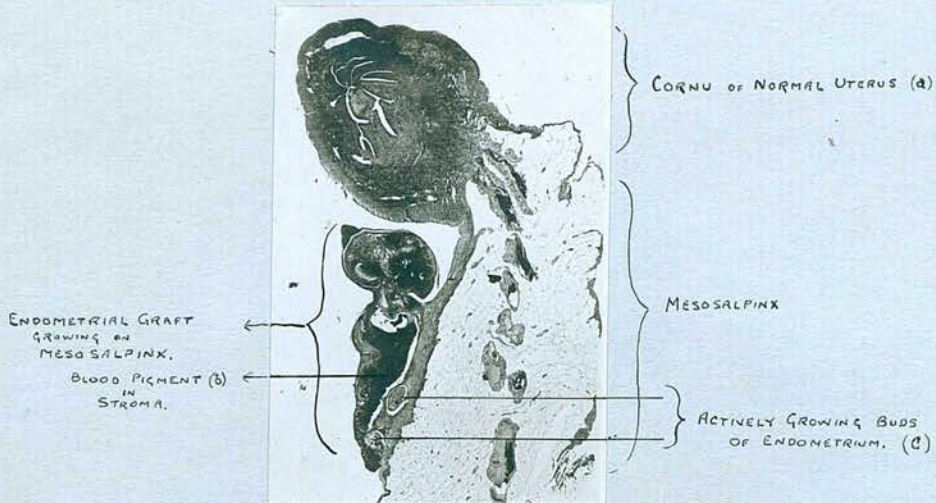
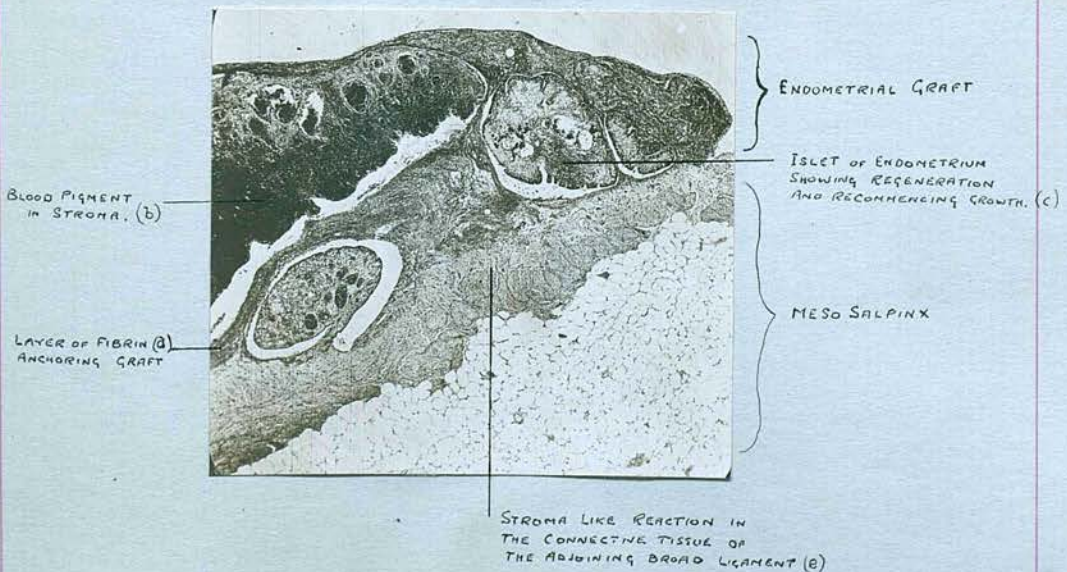


Fig. IX

High Power.





Endometrial Graft on abdominal wall:

Figs. X, XI, XII and XIII.

Fig. X.

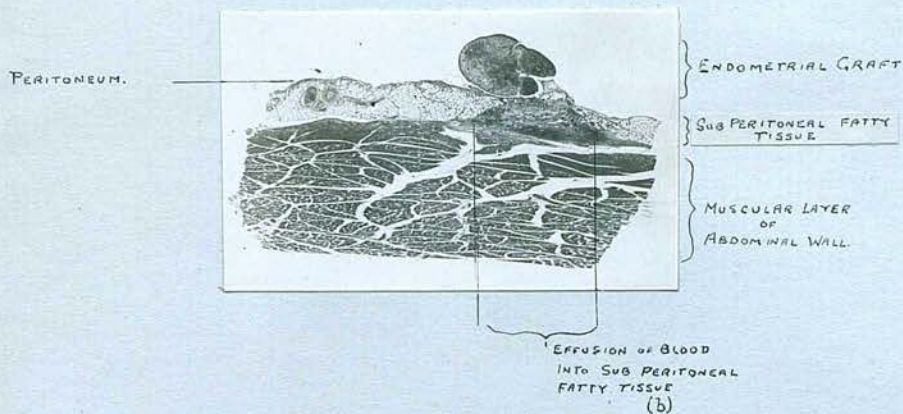


Fig. XI.





Fig. XII. Endometrial Graft on Abdominal Wall  
High Power.

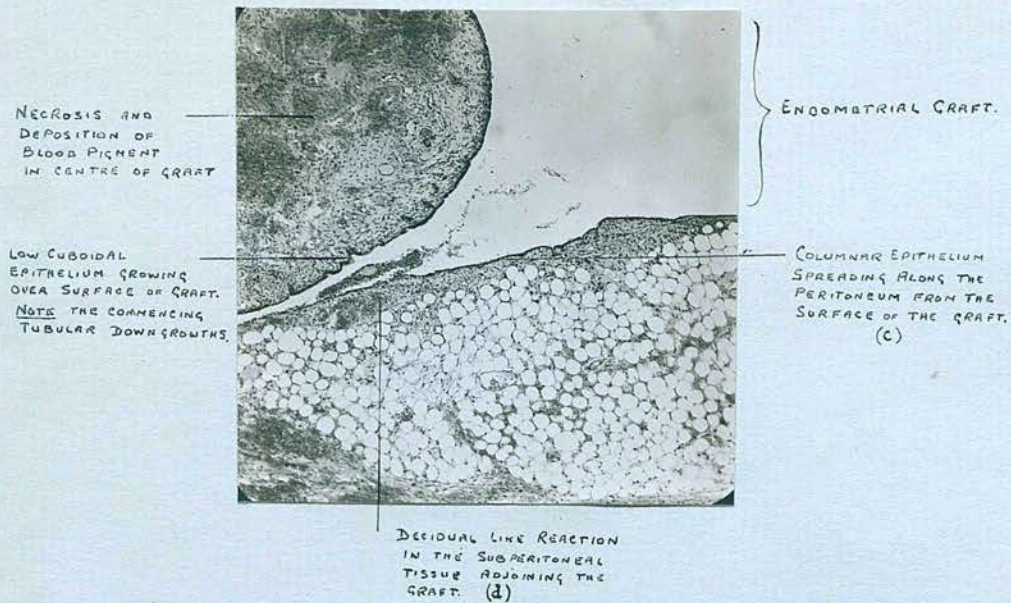
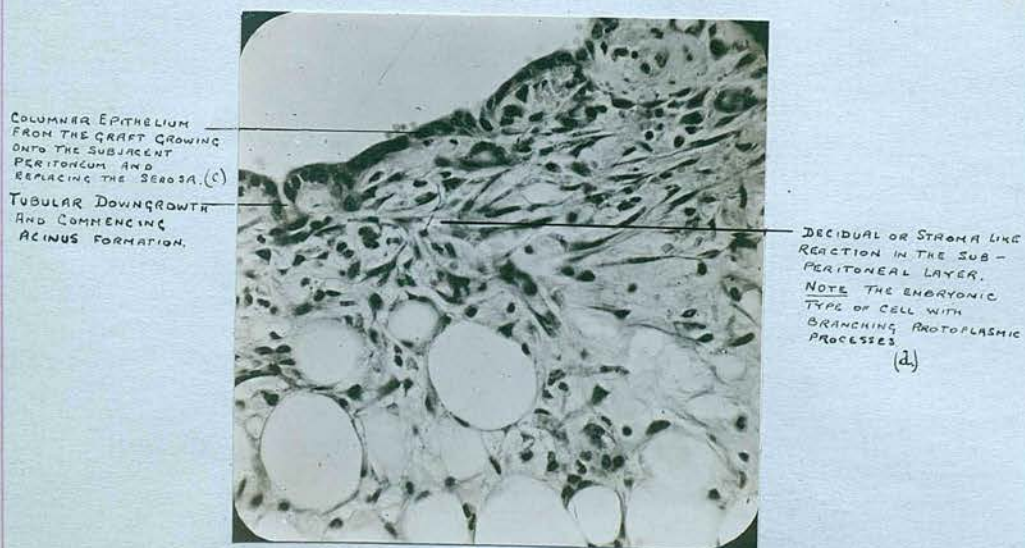


Fig. XIII. Higher Magnification



In the case of this graft the microscopic appearances are practically the same. The whole stroma shows engorgement with blood and blood pigment, the tubular glands have almost entirely disappeared from the epithelial portion, and the columnar epithelium has, in the short space of three days, grown over the entire outer surface of the graft. In one small area at the upper part of the graft, the epithelium is of the tall columnar type and a few tubular glands are present (Fig. XI a), but over the major portion of the surface it is low and cuboidal.

The disintegration of blood in these grafts at an early stage is probably merely due to a tendency to necrosis in the stroma following upon the isolation of the graft, and occurs before the new blood supply is established.

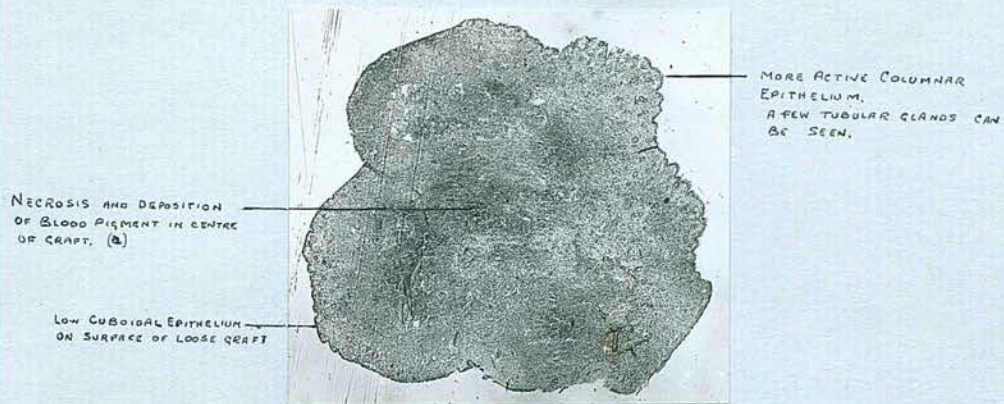
Two very interesting phenomena are to be seen in this section and to a lesser extent in some of the other sections. A well marked effusion of blood can be seen in the sub peritoneal fatty tissue of the abdominal wall in the area to which the graft has become anchored (Figs. X and XI-b), but such an effusion is only present in the immediate vicinity of the graft. This suggests an ability on the part



of the endometrium to stimulate effusion of blood in tissues to which it is adjacent, not only in its normal site in the uterus but in other tissues also. Possibly this effusion is in some way analagous to the menstrual phenomenon or, in the case of rabbits, to oestrus.

The second very interesting observation is the propensity shown by the columnar epithelium of the grafts to migrate onto the adjoining peritoneal surfaces. (Figs. XII and XIII-c) Here we see the very scanty endothelium of the peritoneum replaced by a layer of rapidly growing columnar epithelium which has spread to the peritoneum from the epithelial covering of the graft, displacing the serosal endothelium, and we shall see that in all cases where these endometrial grafts are implanted or implant themselves there is a marked tendency for the columnar epithelium to migrate on to adjoining surfaces. Moreover, we can see (Figs. XII & XIII-d) the scanty connective tissue cells of the sub-peritoneal layer taking on a stroma like form, apparently in response to some stimulus from the migrated epithelium. This phenomenon, again, would appear to be similar to the formation of the "cytogenous mantle" in diffuse adenomyoma as found in the human female.

Loose Graft from peritoneal cavity: Fig. XIV.



The manner in which the columnar epithelium from the endometrial grafts tends to spread rapidly in a thin layer over all adjoining surfaces is exactly similar to the observations of Ebeling and Fischer.<sup>(37)</sup> They grew endometrium in tissue culture and noticed that the columnar epithelium invariably spread in a thin film over the surface of the medium. No such spread was observed in the case of the stroma cells.



The same changes are seen in this graft as in those that had become attached to the viscera. In the central portion there has been disintegration of the red blood corpuscles, with deposition of blood pigment (Fig. XIV-a) and though there is no actual necrosis in the stroma, the connective tissue in the stroma has become homogeneous and cell definition has been lost completely. The periphery is completely covered by rapidly growing columnar epithelium (b) and in the areas of apparently rapid growth this epithelium assumes the low columnar appearance, quite unlike the normal tall columnar cells. The tubular glands in all these grafts show a tendency to disappear at an early stage and in this section they have disappeared almost entirely. In the upper and lower areas a few degenerating tubular glands can be seen (c) near the periphery, but very much smaller and more ill defined than in the normal endometrium.

EXPERIMENT NO. III.

The object of this experiment was to study the behaviour of the endometrial grafts when allowed to continue growth over a slightly longer period, namely, six days instead of three as in the previous experiment. It was also thought that some observations might at the same time be made with regard to the effect of the site on the growth of the grafts, and that growth in a vascular site might be compared with that in an avascular one.

A half grown Angora rabbit was used. Using the same technique as in the previous experiments the left cornu of the uterus was resected, opened along its whole length and the endometrium was shaved off. One piece was stitched by a single catgut ligature to the peritoneal surface of the anterior abdominal wall for comparison with the previous experiment, and a second piece was buried in a stab wound on the anterior surface of the right lobe of the liver, when it was retained in position by two catgut ligatures closing the aperture. The animal made a complete recovery and was killed on the sixth day.

Post Mortem Examination:

On opening the peritoneal cavity there were a few fine adhesions found between the small intestine and upper part of the wound. The graft on the peritoneal surface of the anterior abdominal wall was found quite easily and could be identified by the retaining catgut ligature. It formed a small red rounded nodule, rather smaller than when inserted, firmly adherent to the peritoneal surface. It was not such a deep red colour as the graft in Experiment II, though much darker in appearance than when originally fixed in position. Examination of the liver revealed a pale area surrounding the original stab wound, and on section being made into this area a small pinkish islet of tissue was revealed - apparently the endometrial graft, firmly incorporated with the adjoining liver tissue. Both grafts, with the adjacent tissue, were excised, hardened in 5% formalin and were embedded in paraffin after being passed through spirit and chloroform, as in the other experiment.

Endometrial graft in Liver:

Microscopic examination of this area of the liver at once reveals the presence of endometrium in a state of very active regeneration and growth. A small area is seen growing on the surface of the liver, not very actively, (Fig. 15 ) but deeper down and almost surrounded by liver tissue in an area of endometrium showing high cellular activity. Here the columnar epithelium has in some areas reverted to the normal high columnar type and growth has been sufficiently active to produce both tubular downgrowths and papilliferous buds (Figs. 15 and 16 ). This growth is most active in the centre of the graft as compared with the periphery where both stroma and epithelium are faintly staining and apparently surviving with difficulty. Throughout the section failure of the stroma cells to regenerate as compared with the epithelium is very noticeable, the stroma cells showing cloudy swelling, fragmentation and in areas becoming homogeneous. At the limiting edges of the graft can be seen the same tendency for the columnar epithelium to grow over the external surface as was seen in Experiments I and II. Again in one area can be seen early cyst formation (Fig. 16 - a ).



Between the graft and the liver is a fairly sharp line of demarcation. The adjoining liver tissue has to a certain extent undergone develilisation and degeneration from the trauma of the incision, the cells being large, vacuolated and faintly staining (Fig. 16 - b ). A definite capsule is already beginning to form between the graft and liver tissue and consisting of condensed fibroblasts formed from the graft and not from the liver tissue (Fig. 16 - c ), though the fine fibrous septae between the liver lobules appear to contribute in some degree, and these are thickened in the area adjoining the graft. Over the peritoneal surface of the graft is a well defined fibrous deposit.



Fig. XV.      Endometrial Graft in Liver

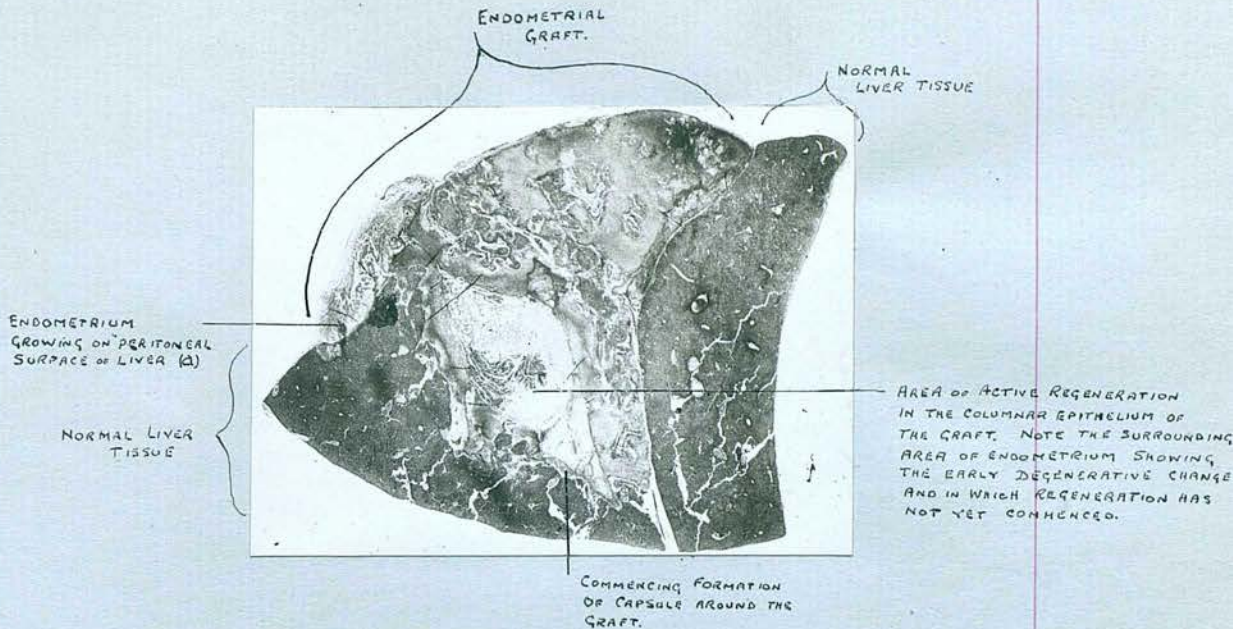


Fig. XVI.      Endometrial Graft in Liver





Fig. XVII.      Endometrial Graft in Liver.  
High Power.

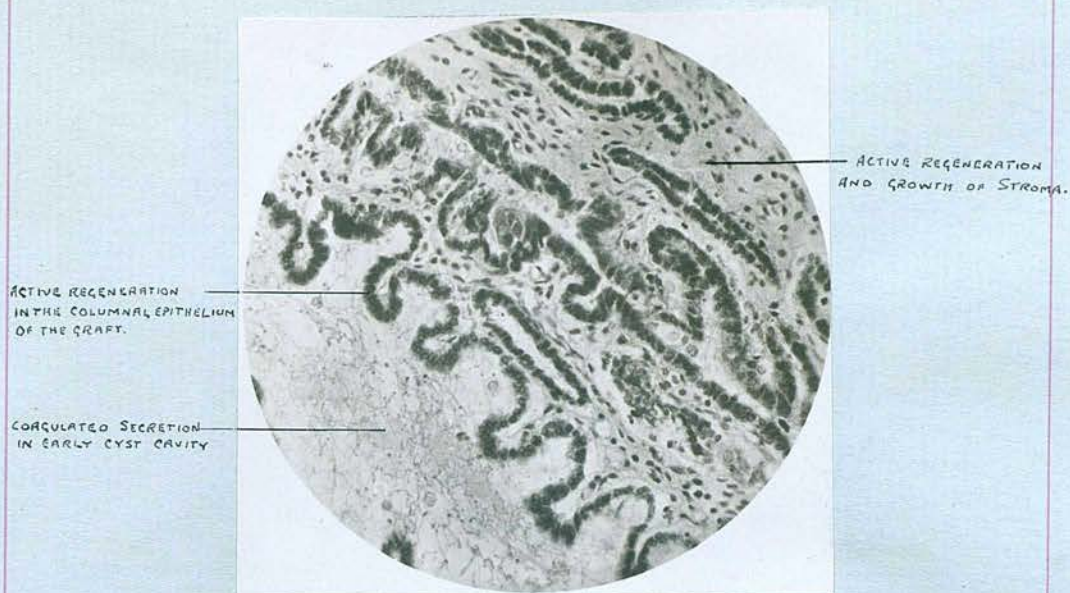
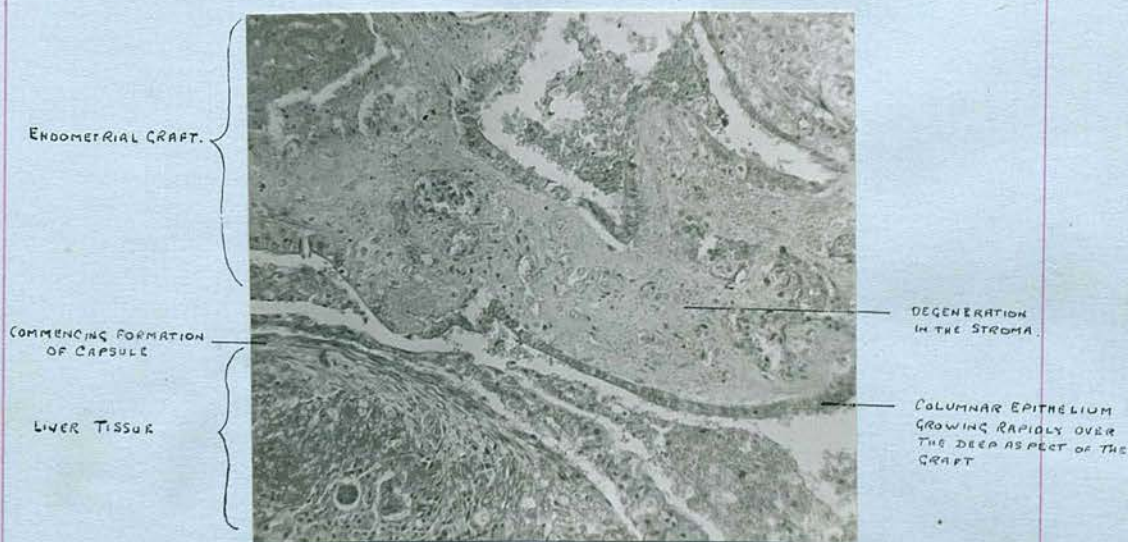


Fig. XVIII.      Endometrial Graft in Liver.  
High Power.





SPECIMENS.

Graft on abdominal wall.

Microscopic Examination:

The changes seen in this section are somewhat similar to those found in Experiment II, but both retrogressive and regenerative changes in the graft have progressed rather further in the additional three days. There has been the same deposition of blood pigment in the stroma but this has been to some extent absorbed and the depth of discolouration by the pigment is decidedly less marked (Fig. 19 - a ). Towards the centre of the graft areas of hyaline degeneration can be seen (Figs. 19-b and 20-b ), but at the periphery regeneration in the columnar epithelium is now well established (Figs. 19-c & 20-c ), and numerous tubular downgrowths from the columnar epithelium can be seen at an early stage of acinus formation. The epithelium though still mainly of low and cuboidal is beginning to show increased activity and in places is approaching the high columnar type (Fig. 20-d ). At the junction of the graft and the peritoneum numerous small adventitious blood vessels may be seen permeating the edge of the graft (Fig. 19 - e ).

Fig. IX.

Endometrial Graft on Abdominal Wall.

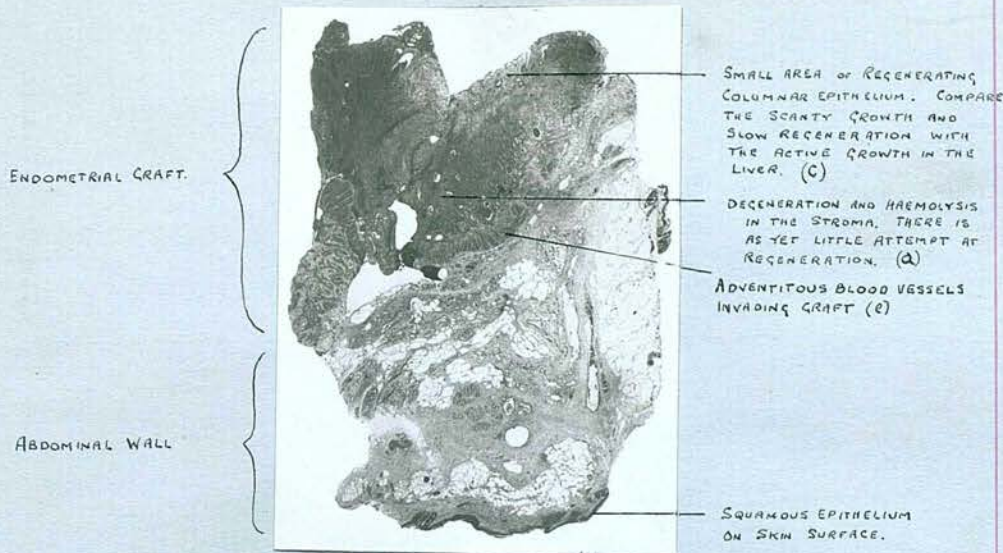
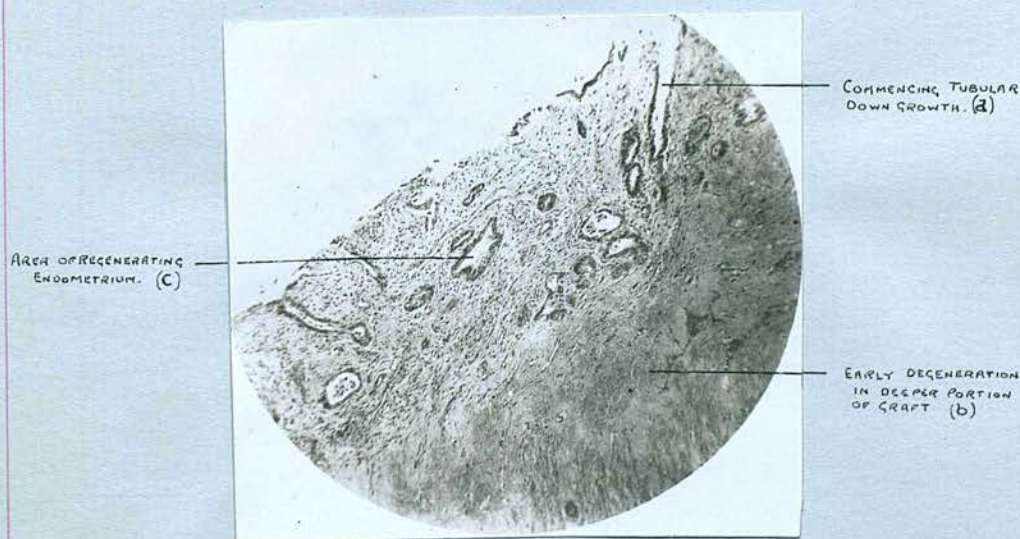


Fig. XX.

Endometrial Graft on Abdominal Wall.

High Power.





EXPERIMENT NO. IV.

For this experiment a medium sized rabbit of unknown age and species was used.

The abdomen was opened in the middle line and all the viscera appeared healthy. About 3 cm. of the left uterine cornu were resected, the cavity laid open and the endometrium stripped off and divided into ten small pieces. These were distributed as follows:-

(a) One piece was fixed by a fine catgut ligature to the anterior rectal wall and the posterior vaginal wall and anterior surface of the rectum were brought together above it by fine catgut stitches.

(b) A portion of the anterior surface of the right uterine cornu was roughened and one piece of endometrium was placed on this area and retained in position by bringing up the mesosalpinx and stitching it to the upper surface of the cornu.

(c) A small piece was stitched to the anterior surface of the right ovary by a single catgut ligature.

(d) Eight small pieces were scattered loose in the pelvic cavity.

The abdomen was closed and the animal made an uninterrupted recovery. It was killed on the ninth day.



Post Mortem Examination:

The abdomen was opened and the original scar found to be well healed. The stump of the left cornu was adherent to the middle of the pelvic colon but there were no other obvious adhesions and all the viscera appeared healthy.

The right ovary was rather dark coloured and bluish in appearance and slightly enlarged. It was irregular in outline and appeared to be multi cystic but the actual graft could not be distinguished. It was removed for examination. The anterior rectal and posterior vaginal walls were adherent and between them a small reddish nodule - apparently the graft - could be seen. No sign was found of the graft on the right uterine cornu. A careful search was made in the peritoneal cavity for the loose grafts. A small bright red nodule about the size of a large pin head was found adherent to the posterior pelvic wall just behind the right uterine cornu (Fig. 21 ). Two other purple coloured nodules were found adherent to the anterior surface of the pelvic colon and about one inch apart. To the upper nodule a loop of small intestine was adherent (Fig. 22 ). No other grafts could be found; those isolated were removed, fixed and embedded.

EXPERIMENT IV.

FIG. XXI.

Endometrial graft on posterior abdominal wall.

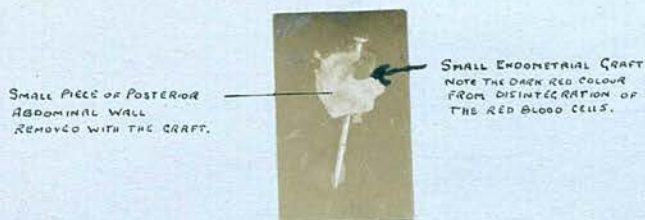


FIG. XXII

Endometrial graft on pelvic colon with adherent small intestine.

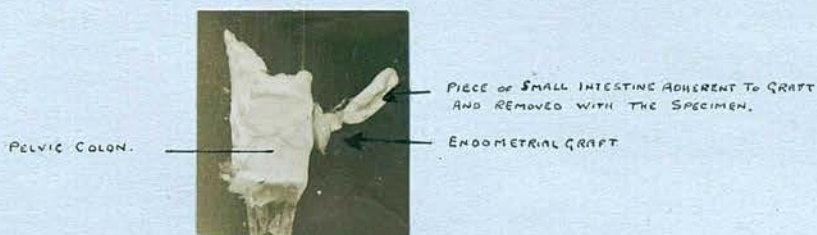
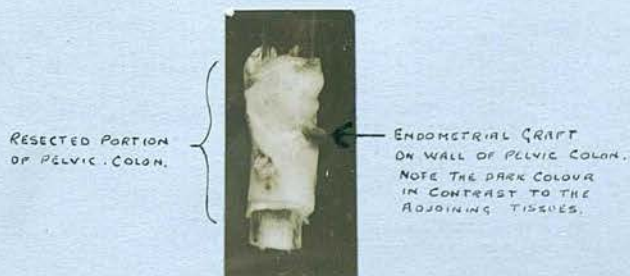


FIG. XXIII

Endometrial graft on pelvic colon.



Microscopic Examination: Figs. 24.

Graft on posterior abdominal wall (Fig. 24.p.62)

Microscopic examination of the graft after a period of growth of nine days shows the same degenerative and reparative processes observed in Experiments II and III, with marked advance in the regenerative process. In this section (Fig. 24 - a) blood pigment is still present in certain areas of the stroma, but in rather more than half the graft it has been absorbed by phagocytic cells. In the lower part of the graft (Fig. 24 -a) the proliferating connective tissue cells can be seen invading the area permeated by blood pigment, the latter being reduced to a number of small islets of a deeper hue. In one area (Fig. 24 -b) there is well marked hyaline degeneration, with loss of cell definition and adjoining this several fissures have appeared in the degenerated stroma (Fig. 24 -c), due probably to the tension exerted by newly formed fibrous tissue around it. At the point where these fissures reach the surface of the graft there is an immediate tendency for the surface columnar epithelium to line both edges of the fissure and to grow down along its whole length, thus invading the stroma, a process well seen in this section (Fig. 24 -d). This phenomenon is seen in other



sections of grafts examined about the ninth day and it would appear to be one of the ways by which the stroma becomes invaded by the epithelial elements, with subsequent cyst formation. At one area invasion of the stroma by tubular downgrowths of epithelium can also be seen (Fig. 24 -e) at a more advanced stage than in Experiment III.

The columnar epithelium covers the whole outer surface of the graft and is now quite firmly established, the cells having reverted to the normal tall columnar type, being close together and having deeply staining nuclei. As already stated at one point deep invasion of the stroma by a tubular downgrowth has occurred (Fig. 24 -e).

At the point of anchorage of the graft to the parietal peritoneum the sub peritoneal layer is seen to be considerably thickened (Fig. 24 -f) in exactly the same way that was observed in Experiment II, and apparently in response to some stimulus from the presence of the endometrium. The connective tissue cells here also have assumed the embryonic form so typical of stroma and decidual cells, a process comparable to the formation of the cytogenous mantle around islets of endometrium in cases of diffuse adenomyoma of the uterine wall.

Endometrial graft on pelvic colon: Fig. 25.p.62.

Here we see a very similar picture though in a slightly more advanced stage. In the process of fixation much of the epithelium has unfortunately been removed, but sufficient remains to indicate the extent of its growth. Practically all the blood pigment has been absorbed and the areas of degeneration have been permeated by a finely cellular stroma (Fig. 25 - a ). The graft has become firmly anchored to the sub serous coat of pelvic colon (Fig. 25 - b ), and the pedicle is becoming invaded by numerous small vessels and lymphatics. The columnar epithelium is well defined and deeply staining and at one point has invaded the centre of the graft (Fig. 25 - c ). This invasion appears to have occurred along a mechanically formed fissure as in the previous section, and does not appear to be due to a normal tubular downgrowth. In the centre of the graft this epithelial invasion has given rise to the earliest stage of cyst formation. It is interesting to observe that although the epithelium, after regenerating and regaining its activity, immediately invades the stroma of the graft, it shows no tendency to invade the adjoining tissues.



EXPERIMENT IV.

FIG. XXIV

Endometrial graft on posterior abdominal wall.

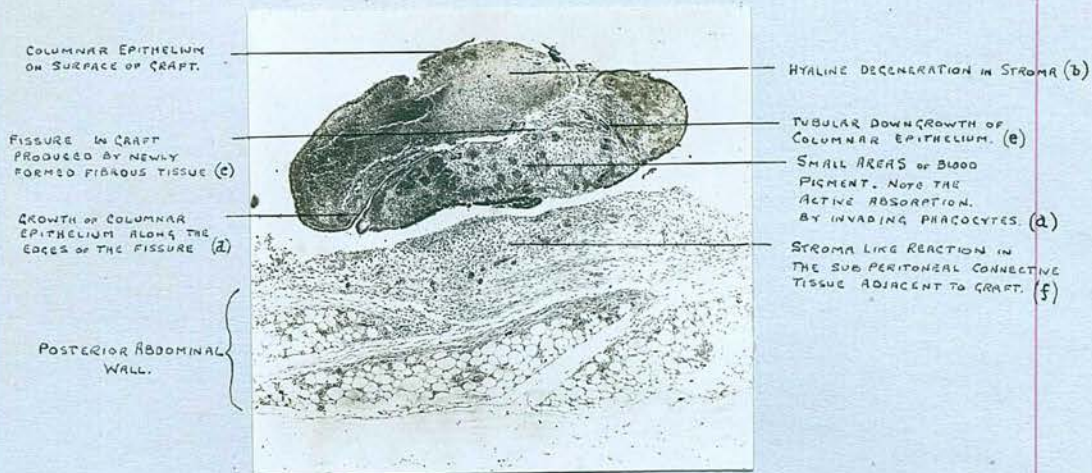
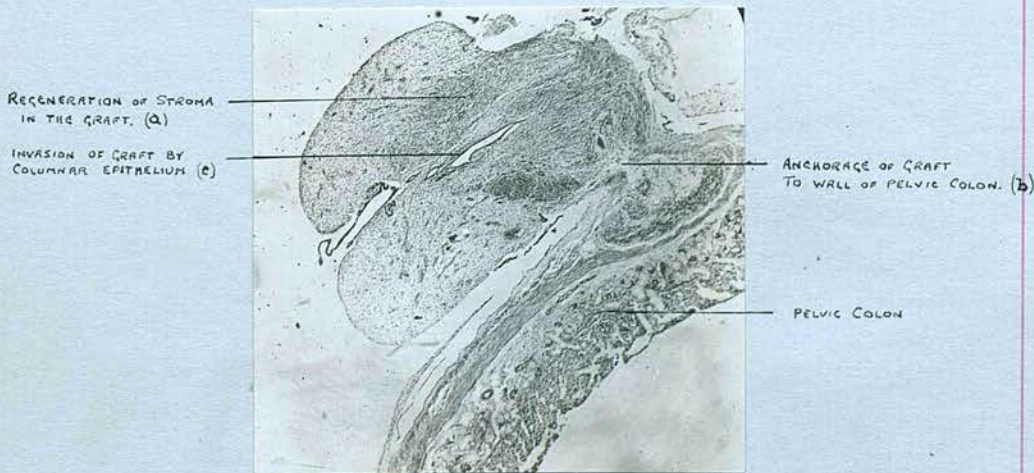


FIG. XXV

Endometrial graft on pelvic colon.





Endometrial graft in ovary: Figs. 26 and 27.p.64

In this instance the endometrium was placed in a stab wound in the ovary and was not fixed merely on the surface. The graft(Fig. 26 - a ) can be seen as a fairly large area of endometrium adjoining and incorporated with normal ovarian tissue (Fig. 26 - b ), which it makes no attempt to infiltrate. Both the ovary and graft have become covered by a fibrinous deposit, probably replacing the blood clot which formed as a result of the stab wound (Figs 26 & 27 -c ). Both stroma and epithelium show active growth, the latter reverting to the normal tall columnar type and lining completely the surface of the graft. In addition, it has begun to grow over the deep surface of the fibrinous deposit (Figs. 26 & 27-c) thus commencing a definite cyst formation (Fig. 27 - d ) and demonstrating yet another way by which cyst formation may be initiated. Absorption of the effused blood pigment is fairly complete and, as in the other specimens in this experiment, renewed activity on the part of the columnar epithelium is shown by well defined tubular downgrowths and early acinus formation.

EXPERIMENT IV.

FIG. XXVI.

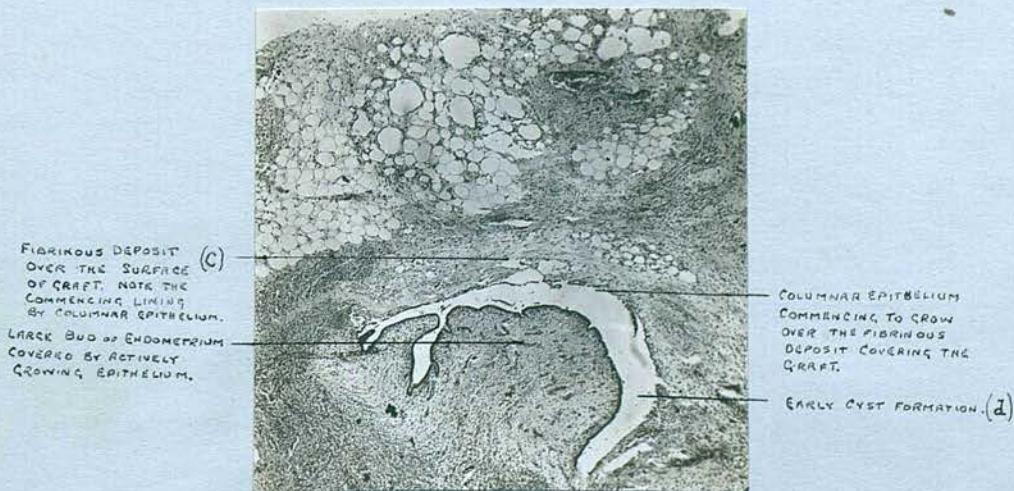
Endometrial cyst in ovary.



FIG. XXVII.

Endometrial cyst in ovary.

High Power



Before proceeding further it would be advisable perhaps to recapitulate the results of these four experiments, and to make some observations on the various stages of growth and tissue reactions in this transplental endometrium.

Firstly, the experiments fully confirm Jacobson's findings, and also those of Bauer<sup>(42)</sup> and Ebeling<sup>(37)</sup> and other experimentors who have been working on this same subject since my early results were first published. Jacobson<sup>(38)</sup> showed that a fragment of endometrium experimentally transplanted in the same animal would continue to exhibit active growth. He was content, however, merely to establish this fact, for he was working in conjunction with Sampson and merely wished, if possible, to substantiate Sampson's theory; he made no investigation of the mode of growth nor of the factors influencing this. Consequently I intend to summarise briefly the various early stages of growth in this transplental endometrium, leading up to the fully formed endometrial cyst, and to show what factors influence this growth and the influence exerted by the transplental endometrium on adjacent tissues.



The phases through which the transplanted endometrium passes appear to be as follows:-

Following its isolation from the uterine cavity the graft tends to become rounded in shape and both the epithelium and stroma undergo retrogressive changes as a result of this sudden cutting off of the blood supply. The stroma undergoes a certain degree of hyaline degeneration and in certain areas actual necrosis may occur. With this there is breaking down of the capillary walls allowing of a diapedesis of blood corpuscles into the interstices between the stroma cells followed by breaking down of the corpuscles and deposition of red blood pigment throughout the stroma. Accompanying these early degenerative changes in the stroma is a concomitant loss of vitality in the columnar epithelium on the surface of the graft. The outer surface becomes smooth and rounded, the tubular glands practically disappear and the tall columnar cells degenerate into the low columnar variety, which during the first few days can be seen in an attenuated state here and there on the surface of the graft. These retrogressive changes appear to occupy between two and three days; if the graft survives then regeneration begins about the third day.

This early period of degeneration in the graft is, in most cases, quickly followed by a process of repair. About the third day there can be seen active proliferation among the islets of surviving stroma cells and commencing invasion by the new cells of those areas which have undergone hyaline degeneration, while at the same time removal of the deposited blood pigment by active phagocytosis commences. Also from the third day onwards, growth of the epithelium, now reduced to a few patches of low cuboidal cells on the surface, recommences, and in these grafts that are not buried beneath the surface but are more or less free in the peritoneal cavity the rejuvenated epithelium grows rapidly over the entire outer surface, possibly as a protective envelope. Once the surface is covered, growth in the epithelial cells tends to crowd them together and by the sixth day we see them returning to the normal high columnar type and at the same time commencing to dip down into the stroma to form acini. By the ninth day regeneration is almost complete, the graft can maintain itself, and its growth as a new and independent structure is assured.

Several other very interesting phenomena were observed. In every case when the graft survived, cyst formation sooner or later resulted, the end result being the formation of a multilocular

cyst adenoma. Close observation revealed several ways in which these cysts originated. Firstly, and rarely, the deep extremity of a tubular gland may be cut off from the surface in the early degenerative processes and later, when active growth recommences this forms a small cystic cavity, which, as we shall see, grows in size along with increase in size of the graft (Experiment III - Fig. 16 ). Secondly, the epithelium on the surface of a loose graft tends after the sixth day to dip down into the stroma forming tubular downgrowths which may become the starting point in the formation of a cyst cavity. This process is aided by the appearance of fissures in the stroma, which form as the result of degeneration in part of the graft and contraction of the newly formed fibrous tissue in the regenerated portions. The columnar epithelium, whose function it appears to be to cover the entire outer surface of the graft, immediately grows down this gap and so produces a long epithelial downgrowth into the centre of the stroma which later produces one or more cyst cavities. This process is beautifully illustrated in Experiment IV - Figs. 24 and 25 Thirdly, in a buried, or partially buried, graft the outer surface of the graft becomes covered over by a layer of fibrin. The inner surface of this fibrinous layer is soon lined by columnar epithelium



and a cyst cavity results, formed on one side by the graft and on the other by a wall of organised fibrin, the whole being lined by columnar epithelium. This process is well illustrated by the cyst in the ovarian graft in Experiment IV. From about the tenth day onwards, as the graft increases in size, these cyst cavities multiply and grow till in a few weeks time we find a typical multilocular cyst adenoma as seen in Experiment I.

Another interesting observation, and one that may throw some light on abnormal endometrial growth in the human female, is the ability of the columnar epithelium to exhibit much more active and varied growth than the stroma. There is, as we have seen in several of these experiments, a tendency for the columnar epithelium once it has regained its activity, to overflow, as it were, from the graft into adjoining serosal surfaces and in so doing to displace the serosal epithelium (Experiment II). There is no such tendency for migration shown by the stroma, which appears always to remain in the original site. An observation of importance is the reaction produced by this migratory epithelium on the subjacent connective tissue cells (Experiment II - Fig. 13 )which can be seen changing from the normal connective

tissue type to an embryonic type similar in many respects to the normal stroma or decidual cell. This would show that the uterine-columnar epithelium has an inherent capacity for influencing the connective tissue cells in its vicinity, such influence being the production of a cushion for itself in the form of a soft spongy stroma. Obviously the epithelium may migrate without any migration of the stroma, but when this occurs the migratory epithelium quickly exerts its influence on the subjacent connective tissue in order to produce a new stroma, very similar to that found normally in the uterine cavity. It would tend to show that the epithelium migrates much more readily than the stroma, if indeed the stroma migrates at all, and that this migratory epithelium has the power to create a new stroma for itself from the connective tissue in its vicinity. This strongly suggests that in diffuse adenomyoma of the uterine wall, as found in the human female, the cytogenous mantle of stroma like cells around the islets of endometrium may not be formed of migrated stroma, but is formed from the connective tissue cells in the uterine wall as the result of an influence exerted by the wandering columnar epithelium.

In this series of experiments only one, Experiment III, was performed in order to demonstrate the influence of environment on the growth of the grafts. In this experiment one graft was placed in the liver - one of the most vascular organs in the body, and a similar graft was fixed to the peritoneal aspect of the abdominal wall. The result revealed very much more active growth in the graft implanted in the vascular area, the difference being so marked that there could be no doubt regarding this fact, and later experiments, as we shall see, confirm this result. It can thus be seen that one of the most important factors influencing the growth and activity of "ectopic" endometrium is the site or organ on which it becomes implanted and that the more vascular the point of influence the greater will be the chances of survival of the graft, and if it survives, the more active will its subsequent growths become.

It is perhaps unfair to look for signs of the continuance of a menstrual process in these grafts since oestrus in the rabbit is hardly comparable to menstruation in the human being. Experiment I, however, does show the presence in the cyst cavity of an exudate containing a large quantity of blood cells, polymorphs and desquamated epithelium similar in all respects to the normal oestrus secretion. As



this experiment was performed in the early spring it is perhaps permissible to suggest that an oestrus cycle occurred shortly after the performance of the experiment and that the endometrium in the grafts participated.

That the endometrium tends to exert some influence on adjoining tissues is shown both by its tendency to promote a decidual or stroma like reaction on nearby connective tissue, and also by the tendency for effusion of blood to occur in such areas. This is well shown in Experiment II Fig. 11, where there is a distinct effusion of blood in the sub-peritoneal layer below the graft and to a lesser extent in Experiment IV. Exactly the nature of this blood effusion we cannot say, but it seems not unlikely that it is in some way closely related to the oestrus process.

Lastly, I would like to point out that in these experiments, though migration of epithelium on to adjoining surfaces may occur, yet no evidence of invasion of adjoining tissues by either the epithelium or stroma is demonstrable.

OBSERVATIONS ON THE LENGTH OF LIFE  
OF SIMPLE AUTOGENOUS ENDOMETRIAL GRAFTS.

EXPERIMENT NO. V.    March 5th 1925.

For this experiment a large well nourished and healthy white Angora rabbit of unknown age was used. Adopting the same technique as in the former operations, a mid line incision from the symphysis pubis to the xyphic sternum was made. The uterine cornua were normal and healthy and there was no evidence of recent pregnancy.

Approximately between 3 cm. and 4 cm. of the right uterine cornu were resected in the usual way. This was opened along the entire length, the endometrium exposed and shaved off, and this was cut into pieces of the same size approximately as those used in the previous experiments. A stab wound was then made in the right lobe of the liver as in Experiment No. III, and one piece of endometrium was buried in the stab wound and was retained in position by a continuous catgut suture closing the incision. Another piece was stitched in the recto-vaginal septum by one catgut stitch passing through the anterior rectal wall, graft and posterior vaginal wall. In doing this the rectal wall was opened accidentally and was closed with continuous through and through sutures. Six pieces of endometrium were then scattered in the lower part of the abdominal



cavity and the abdomen was closed.

Ten months later - two hundred and ninety days after the operation - the rabbit died.

Post Mortem Examination. 21st December 1925.

The abdominal scar was found healthy and well healed, but a few fine adhesions were found between the small intestine and the scar. A strand of omentum was found adherent to the right lobe of the liver at the site of the stab wound and this appeared to have strangulated the bowel, which was distended above and collapsed below the band.

Examination of the liver revealed a pale whitish area at the point where the graft had been buried and in the liver substance at this point could be seen a small cyst about 1 c.m. in diameter showing on both the superior and inferior surfaces. (Fig. 28 ) There was no distortion of the shape of the liver in this area and the surrounding liver tissue appeared quite healthy. The cyst together with adjoining liver tissue was removed, fixed, embedded and cut in serial sections.

After fixation the specimen excised from the liver was split open. On incising it a cystic cavity was revealed with a septum dividing it into

two distinct loculi. In size it was rather more than 1 cm. in diameter and was completely filled with a softish white pultacious material. The cyst wall could be seen quite distinctly separating the cyst in front and behind from normal liver tissue. Above and below it extended to the peritoneum covering of the liver. (Fig. 28 ).

Examination of the lower abdomen showed all the viscera to be healthy. Both ovaries and the left uterine cornu were small and healthy and the right cornual stump was well healed. Growing on the anterior surface of the left cornu of the uterus and lightly adherent to the anterior wall of the pelvic colon was a small round tumour, pale pink in colour and about 3 m.m. in diameter (Fig. 29 ). It was very soft in consistence and on closer examination, though the walls were not translucent, it appeared cystic. This "tumour" along with part of the left uterine cornu and the adherent portion of the pelvic colon was excised, fixed and embedded for section. In the recto-vaginal space and adherent to both rectum and vagina was a small multilocular cyst about the same size as that found on the uterine cornu but with thin translucent walls. It also was excised and kept for examination.

Macroscopic appearances.

Endometrial cyst in liver.

Fig. XXVIII.



ANTERIOR BORDER OF LIVER SHOWING NORMAL LIVER TISSUE.  
ENDOMETRIAL CYST IN LIVER CONTAINING  
WHITE PULTACEOUS MATERIAL.  
NORMAL LIVER TISSUE.

THE ABOVE PHOTOGRAPH SHOWS THE ENDOMETRIAL CYST IN THE LIVER. THE SPECIMEN HAS BEEN CUT OPEN AFTER HARDENING INTO TWO HALVES, AND SHOWS THE CYST IN SECTION.

Fig. XXIX. Endometrial cyst on pelvic colon.



ENDOMETRIAL CYST  
ATTACHED TO PELVIC COLON  
POSTERIORLY AND TO UTERUS  
BELOW.

LEFT HORN OF UTERUS  
LYING IN FRONT OF  
PELVIC COLON.

PELVIC COLON.

LEFT HORN OF UTERUS.

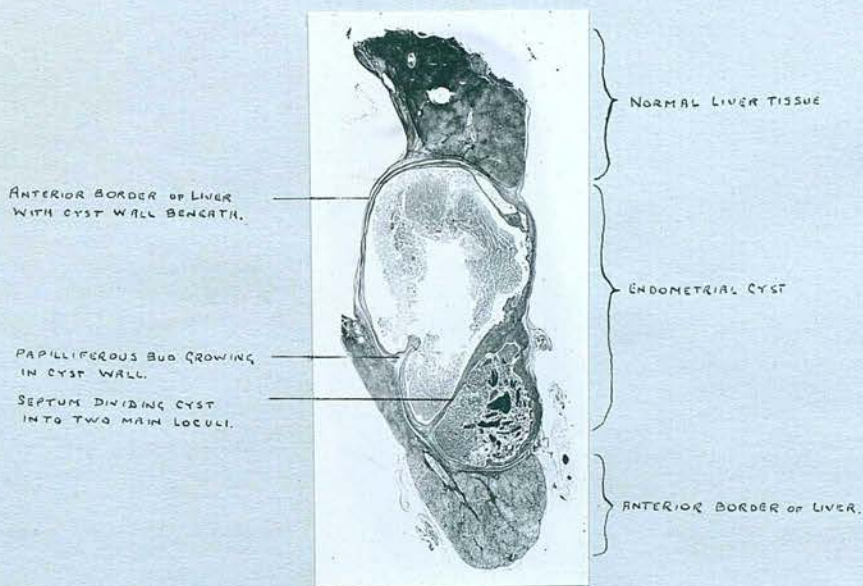
PELVIC COLON.

THE ABOVE PHOTOGRAPH SHOWS A LOOP OF PELVIC COLON RUNNING VERTICALLY DOWNWARDS. RUNNING OBLIQUELY ACROSS AND IN FRONT OF THE COLON IS THE LEFT UTERINE CORNU. ATTACHED BOTH TO THE UTERUS AND THE PELVIC COLON IS THE ENDOMETRIAL CYST.



Microscopic Examination.

Endometrial Cyst in Liver. Fig. XXX.



ABOVE IS A LOW POWER PHOTOGRAPH OF THE ENDOMETRIAL CYST IN THE LIVER. IT IS DIVIDED BY AN OBLIQUE SEPTUM INTO A LARGE UPPER LOCULUS AND A SMALLER ONE BELOW. A WELL DEFINED CYST WALL CAN BE SEEN WITH ONE OR TWO PAPILLIFEROUS BUDS GROWING INTO THE CYST CAVITIES. ON THE LEFT SIDE IS THE SUPERIOR SURFACE OF THE LIVER AND TO THE RIGHT THE INFERIOR SURFACE. ABOVE AND BELOW IS NORMAL LIVER TISSUE.

Here we see a well defined bilocular cyst situated near the anterior border of the liver. It has grown in size until above and below it has reached the peritoneal surface but anteriorly and posteriorly normal liver tissue can be seen bounding it. There is a complete lining of columnar epithelium which varies greatly in type, being tall and columnar in those areas where a well defined stroma is present, and low and cuboidal over large areas of the cyst wall. Both stroma and epithelium show more vigorous growth in the areas bounded by normal liver tissue, for in those parts of the cyst bounded by peritoneum stroma is practically absent and the epithelium is reduced to a layer of very low cuboidal cells. Again this tends to demonstrate the dependence on blood supply for growth in ectopic endometrium, and a comparison might be made between this tarry ovarian cyst where typical endometrium consisting of tall columnar epithelium and cellular stroma is usually only found at the inner pole where the tarry cyst is adherent to the uterus.

Growing from the septum and the cyst walls several papilliferous buds can be seen projecting into the cyst cavities and in the cyst walls there are several well defined small daughter cysts. A mass of cellular debris may be observed in the cyst cavities consisting of homogenous material



containing red blood cells, round cells and some large phagocytic cells.

Fig. XXXI.

Endometrial Cyst in Liver.

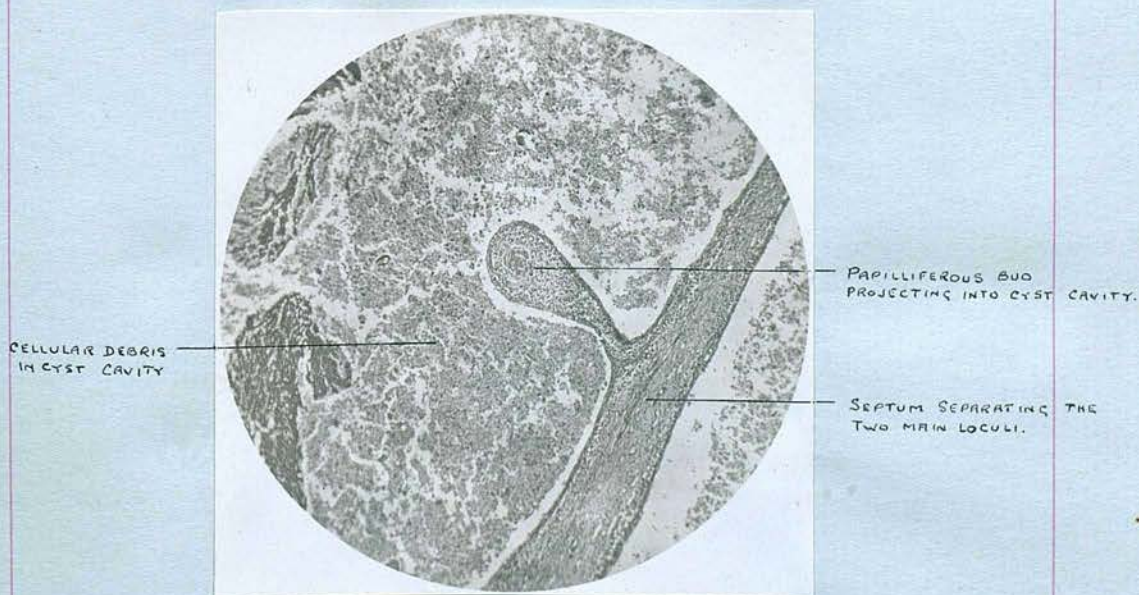
Cellular portion of  
cyst wall.



Endometrial Cyst in Liver.

Septum dividing cyst  
with papilliferous  
bud.

Fig. XXXII





Under high power the cellular portions of the cyst wall can be seen to be lined by very tall columnar cells with nuclei situated at the base. Though there is a suggestion of a basement membrane here and there, actually no true basement membrane is present. As is shown by Fig. the columnar epithelium is in places reduced to a very thin and attenuated layer, partly as the result of pressure within the cyst and partly on account of the avascular subjacent tissue. In places the tall columnar epithelium shows well marked cilia projections. The stroma varies considerably. In all active portions of the cyst wall it is moderately cellular but is never present in any great thickness. In the portions of cyst wall that are thin and are not supported by liver tissue the stroma has in places disappeared, or has become reduced to a layer one cell thick. The remainder of the cyst wall, apart from the epithelium and stroma, consists of unstriated muscle fibres, fibrous tissue, blood vessels and lymphatics, though in the very thin portions fibrous tissue only is present. In the two portions adjoining the liver tissue the capsule is strengthened by some connective tissue derived from the connective tissue septae between the liver lobules.

Endometrial Graft on Uterine Cornu. Figs  
XXXIII &  
XXXIV

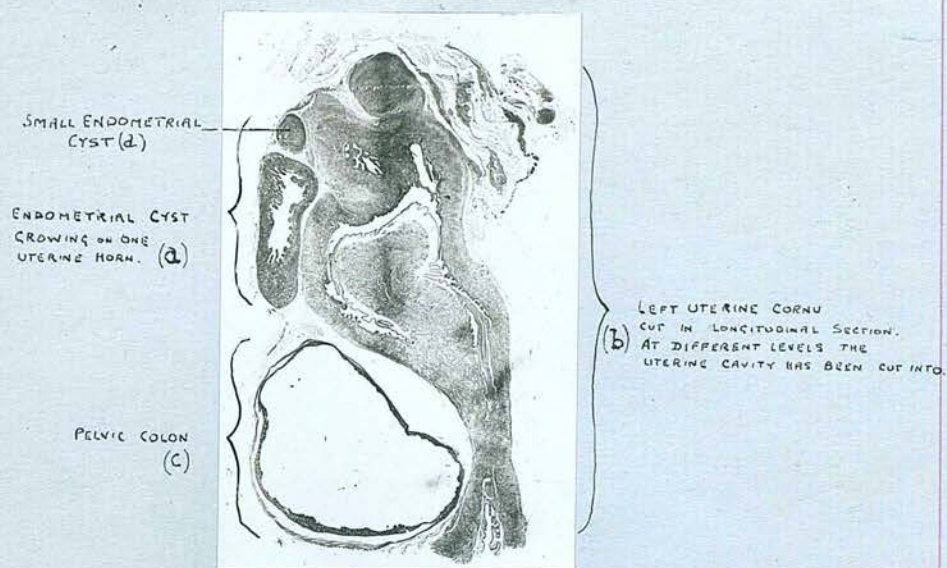
Fig. 33 shows a section taken through the uterine cornu<sup>(b)</sup> with the endometrial cyst<sup>(a)</sup> on its anterior surface, and below can be seen the adherent pelvic colon.<sup>(c)</sup> It is rather different in type from the previous cyst in the liver, being much smaller in size, and having a thicker and more cellular cyst wall. At first sight it appears unilocular but closer observation reveals a small loculus with relatively thick walls and a very small cyst cavity just above the main cyst.<sup>(d)</sup>

Under higher power Figs 34 and 36 the cyst can be seen to be lined by tall columnar epithelium with basally placed nuclei; in places cilia can be distinguished and many papilliferous buds project into the cyst cavity. The stroma, unlike that in the liver graft, is very thick and highly cellular throughout and shows a few gland tubules. In the deeper part it is composed of spindle cells connected together by a fine reticulum with unstriated muscle and vascular connective tissue beyond, the whole being permeated by a large number of small blood vessels and lymphatics.



FIG. XXXIII.

Endometrial cyst on peritoneal surface of Uterus.



THE ABOVE SECTION SHOWS THE ENDOMETRIAL CYST ADHERENT TO THE UTERUS POSTERIORLY AND TO THE PELVIC COLON BELOW

FIG. XXXIV.

High Power.

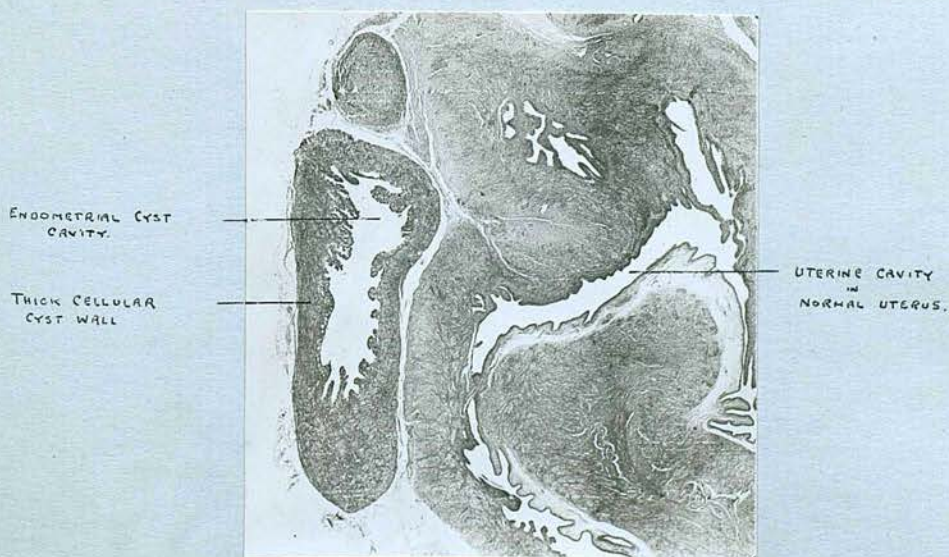
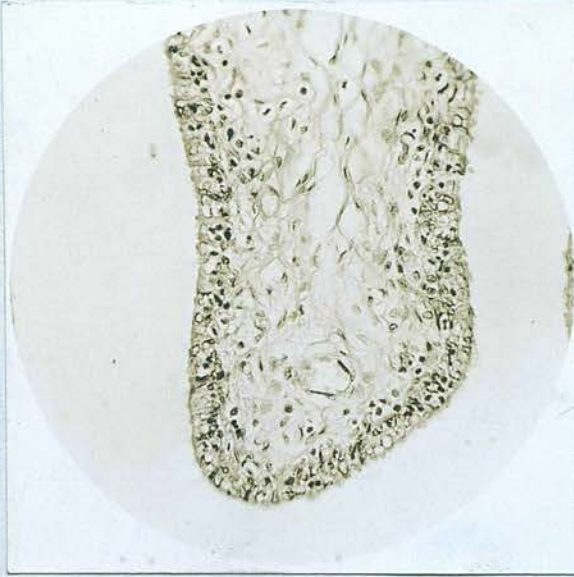


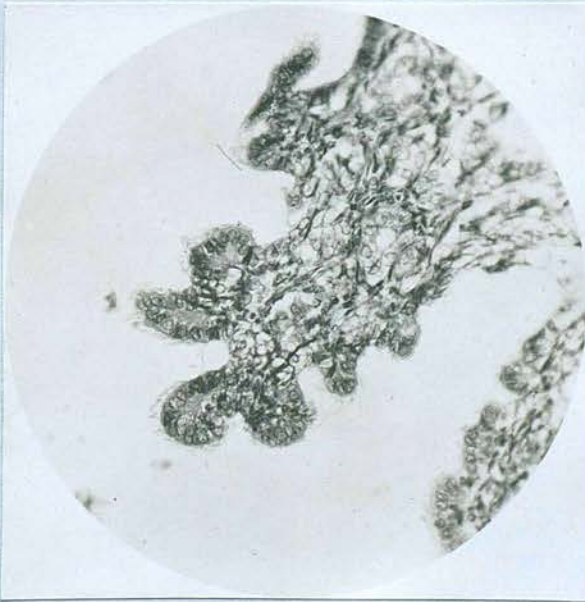


FIG. XXXV.      Endometrium from normal uterine cavity



THE ABOVE MICROPHOTOGRAPH SHOWS THE NORMAL ENDOMETRIUM TAKEN FROM THE UTERUS OF THE RABBIT USED FOR THIS EXPERIMENT. COMPARE THIS WITH THE ALTERED ENDOMETRIUM IN THE ENDOMETRIAL CYST AS SEEN BELOW.

FIG. XXXVI.      Epithelial lining of endometrial cyst.



A PORTION OF THE EPITHELIAL LINING OF THE ENDOMETRIAL CYST GROWING ON THE UTERINE CORNU. NOTE THE ALTERATION IN CELL TYPE. THE COLUMNAR EPITHELIUM IS IRREGULAR AND THE NUCLEI LARGER THAN NORMAL, WHILE THE STROMA CELLS HAVE BECOME MORE CROWDED TOGETHER. THE APPEARANCE CLOSELY RESEMBLES THAT OF A MALIGNANT PAPILLIFEROUS OVARIAN CYST ADENOMA.

Figs. 35 and 36 are shown side by side, the former being a high power micro photograph of the normal endometrium in the same rabbit, and the latter the "altered endometrium" in the cyst wall. As can readily be seen the epithelium lining the cyst has become very irregular and shows many small branching processes. The epithelium is still limited to a single layer, the nuclei are still situated basally and there is no irregular mitosis though the appearance is not unlike that seen in a papilliferous ovarian cyst. Unlike the cyst in the liver there is no evidence of any secretion or desquamation into the cyst cavity.

This experiment tends to show that transplanted endometrium will continue to grow for a very long time, perhaps indefinitely during the life of the animal. It also confirms the previous observation that the rate and extent of growth is dependent on the blood supply at the point of implant, for again we find much more active growths in the graft in the highly vascular liver tissue than in the one on the comparatively avascular anterior surface of the uterus. The reason for the great difference in the type of growth in these two grafts forms an interesting speculation. In all probability a poorer blood supply in the case

of the second graft has resulted in slower growth, but this slow growth has allowed more time for the cellular elements to become established. A restricted blood supply has resulted in a lessened secretion into the cyst cavity and so has prevented the occurrence of pressure atrophy that is so apparent in the cyst implanted in the liver.



EXPERIMENT NO. VI.

The longest period over which I have been able to observe growth in these endometrial grafts is 760 days, rather more than two years.

A large Angora rabbit of unknown age was used for the experiment. Under ether anaesthesia, and using the same technique as in the previous experiments, the abdomen was opened by a mid line incision about five inches long. All the abdominal viscera were healthy and the uterine cornua were slightly larger and thicker than normal, suggesting that the animal had recently been pregnant.

Approximately 4 cms of the inner end of the right uterine cornu were excised. This was opened up and the endometrium was shaved off. A stab wound was made in each ovary and into these was inserted a small piece of endometrium; in each ovary the graft was secured by catgut ligatures and the site of the incision was covered over by peritoneum. A portion of the anterior surface of the left uterine cornu was scarified and to this area a third piece of endometrium was attached by catgut ligature.

The animal made a good recovery and lived for over two years. At the end of this

time it had become very decrepit, apparently from old age, so was killed 760 days after this operation.

Post Mortem Examination:

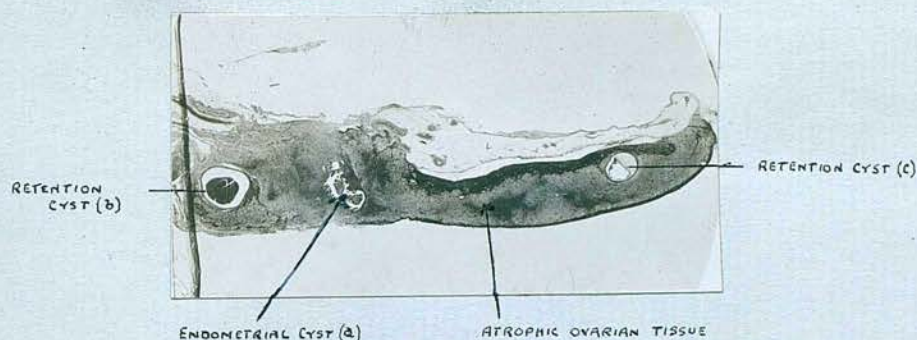
The abdominal cavity and viscera appeared healthy and there were very few adhesions present. A hydrosalpinx had formed in the occluded end of the right cornu, but there was no sign of the graft which had been fixed to the left cornu.

Examination of the left ovary, which appeared rather small and atrophic, revealed a small blackish cyst about the size of a small pea in the ovarian substance and projecting slightly from the surface. The right ovary was very similar in appearance and at the lower pole could be seen a small blackish cyst very similar to that seen in the left ovary. There were no adhesions to the ovaries and a careful examination of all the pelvic organs and lower abdomen failed to reveal any sign of any further implants. Both ovaries were excised, fixed in formalin and embedded in paraffin for serial sections.

Microscopic Examination:

Endometrial Cyst in Right Ovary. Low Power.

FIG. XXXVII.



ABOVE IS SEEN A LONGITUDINAL SECTION THROUGH THE OVARY  
THE SMALL ENDOMETRIAL CYST CAN BE SEEN IN THE CENTRE (a)  
AT EITHER END IS A RETENTION CYST (b & c)

The low power shows a section through the whole length of the ovary. About the middle a small endometrial cyst can be seen lined by fairly active endometrium. The ovary contains two follicular retention cysts but no graafian follicles or corpora lutea can be seen and the ovarian tissue is obviously atrophic and similar to the post menopausal ovary of the human female.



High Power.ATROPHIC OVARIAN  
TISSUEENDOMETRIAL GRAFT  
WITH TWO SMALL CYST  
CAVITIESATROPHIC OVARIAN  
TISSUE.

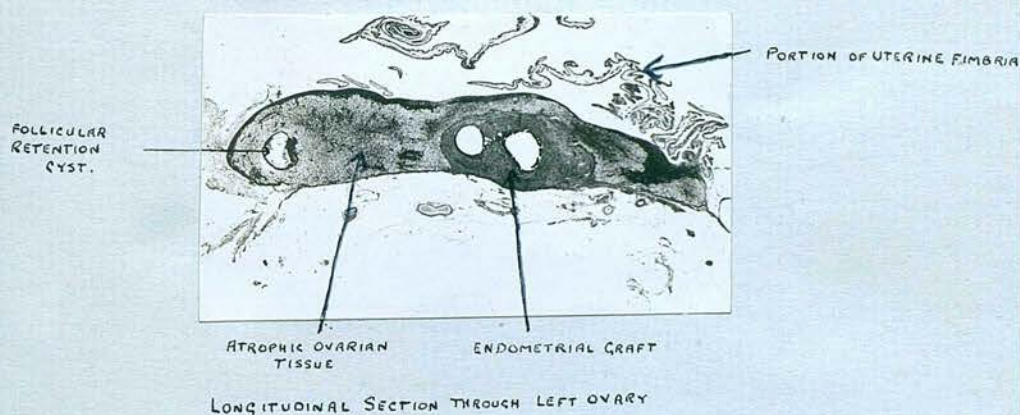
Under high power the islet of endometrium can be distinguished quite easily. It can be seen to contain two small cystic cavities lined by columnar epithelium surrounded by a wide area of stroma. Both epithelium and stroma tend to be atrophic and show much less cellular activity than in the previous experiments. The surrounding ovarian tissue is also very atrophic and its reproductive function appears to have ceased.



FIG. XXXIX.

Left Ovary.

Low Power.

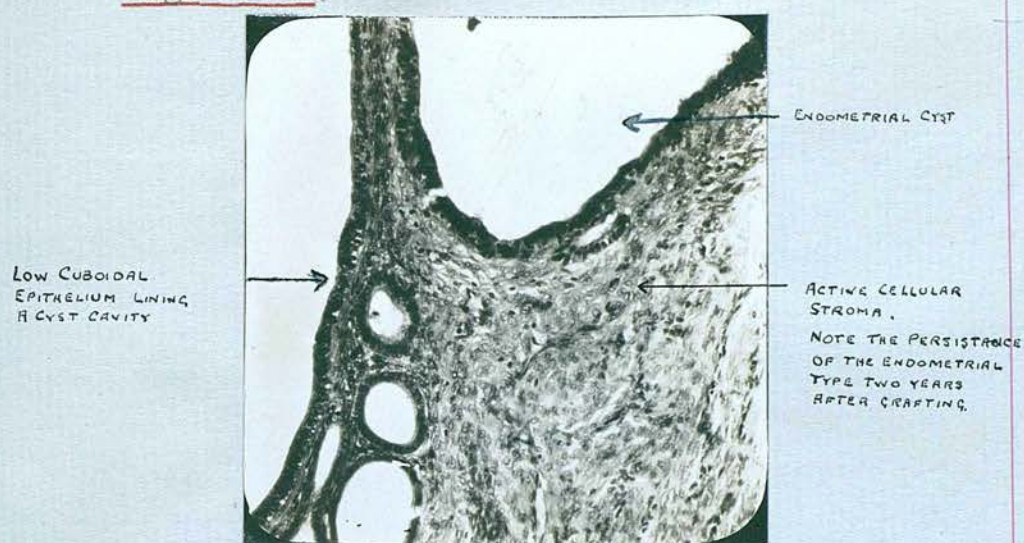


In the left ovary the endometrial graft is much larger and can be seen occupying the centre of the ovary. It contains two small cyst cavities and a relatively large area of stroma which is clearly defined from the ovarian tissue. The ovarian tissue appears inactive and contains neither graafian follicles nor corpora lutea.



FIG. XL.

High Power.



Under high power a persistence of the endometrial type of cell can be seen in the graft. The cyst cavities are lined by epithelium which tends to assume the low cuboidal type - in all probability a retrogressive change due to atrophy in the ovary - but the stroma is still quite cellular and is easily distinguishable as such.



Before proceeding further with these experiments it is perhaps advisable briefly to summarise the main results that have been obtained.

It has been shown very definitely that in the case of the rabbit autogenous endometrial transplants will, in all cases, establish themselves in the new site and there continue to exhibit active growth. This growth in all cases is in the nature of cyst production, the resultant cyst being always a multilocular cyst adenoma. The type of growth of both the columnar epithelium and the stroma may vary between wide limits depending on such factors as the site of implantation, the vascularity of the area in which it is embedded and the length of time during which the implants are allowed to grow, and it would appear that once this transplanted endometrium has attained to independent growth, it will continue to grow throughout the lifetime of the host. The extreme difficulty of keeping rabbits alive for very long periods has prevented observation over a longer period than two years, but Experiment No. VI shows that the graft will maintain independent growth throughout the life of the host and that, with increasing age of the animal, they will

undergo the retrogressive senile changes associated with the normal reproductive tract.

Though multilocular cyst adenomata have been produced it cannot be said that these "tumours" resemble in any marked way any of the types of "adenomyoma" or "endometrioma" as found in the human female. In both the uterine and extra uterine varieties in the human female, whether diffuse or nodular, the endometrial like growths are never in the nature of isolated cysts. There is always some degree of non malignant permeation by this endometrial like tissue to which the term "endometriosis" has been aptly applied, and though all these experiments demonstrate the ability of "ectopic" endometrium to continue active growth, they do not reproduce this feature of permeation of the adjoining tissues so typical of "endometriosis".

It was thought that by variation of other factors in the experiments it might be possible to produce in the rabbit this feature of permeation, and with this in view the following further experiments were undertaken.

EXPERIMENT NO. VII.

An almost full grown female rabbit of unknown species was used for this experiment.

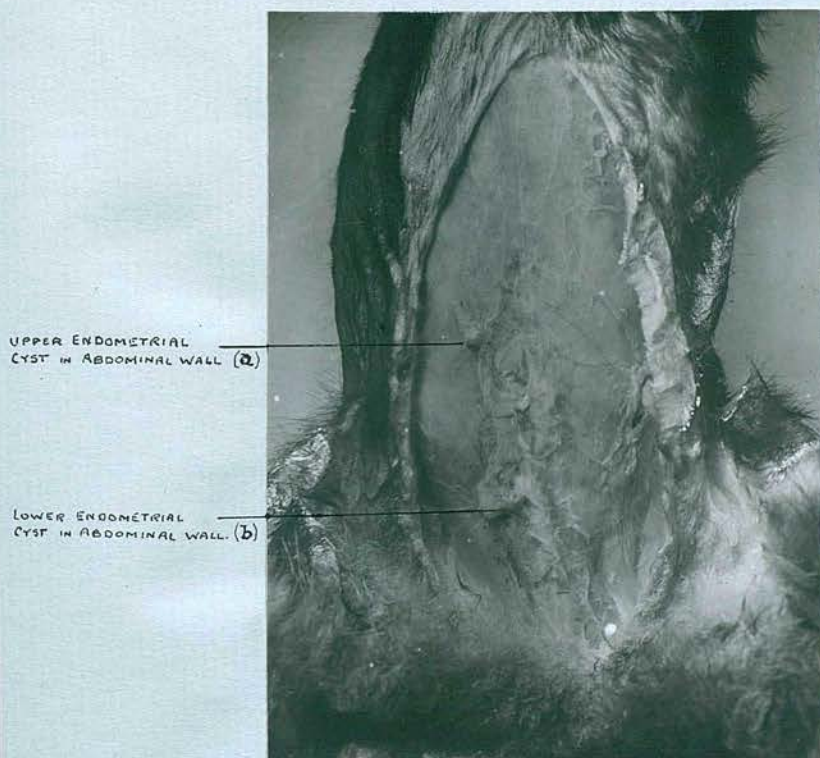
Under ether anaesthesia a mid line incision about 4" long was made in the lower abdominal wall and the peritoneal cavity opened. The abdominal viscera were healthy and the pelvic organs appeared normal. Both uterine cornua were resected and the endometrium shaved off as in the previous experiments. Several pieces were scattered in the lowered part of the peritoneal cavity and the peritoneum was then closed. The rectus sheath on the right side of the incision was reflected and the rectus muscle exposed and two pieces of endometrium were buried in the rectus muscle and retained there by catgut sutures. The abdominal wall was then closed. It was thought that in this way it might be possible to reproduce that type of adenomyoma occasionally found in the abdominal scar in women following Caesarean section or fixation operation.

Three hundred and eighty eight days later the rabbit was accidentally killed by falling out of its cage.



Macroscopic appearance.

FIG. XLI.      Endometrial cysts in abdominal wall.



THE ABOVE PHOTOGRAPH WAS TAKEN AFTER THE SKIN HAD BEEN REFLECTED TO EXPOSE THE RECTUS SHEATH. THE TWO ENDOMETRIAL CYSTS IN THE MUSCULAR LAYER CAN BE SEEN BULGING UNDER THE APONEUROSIS.

Post Mortem Examination.

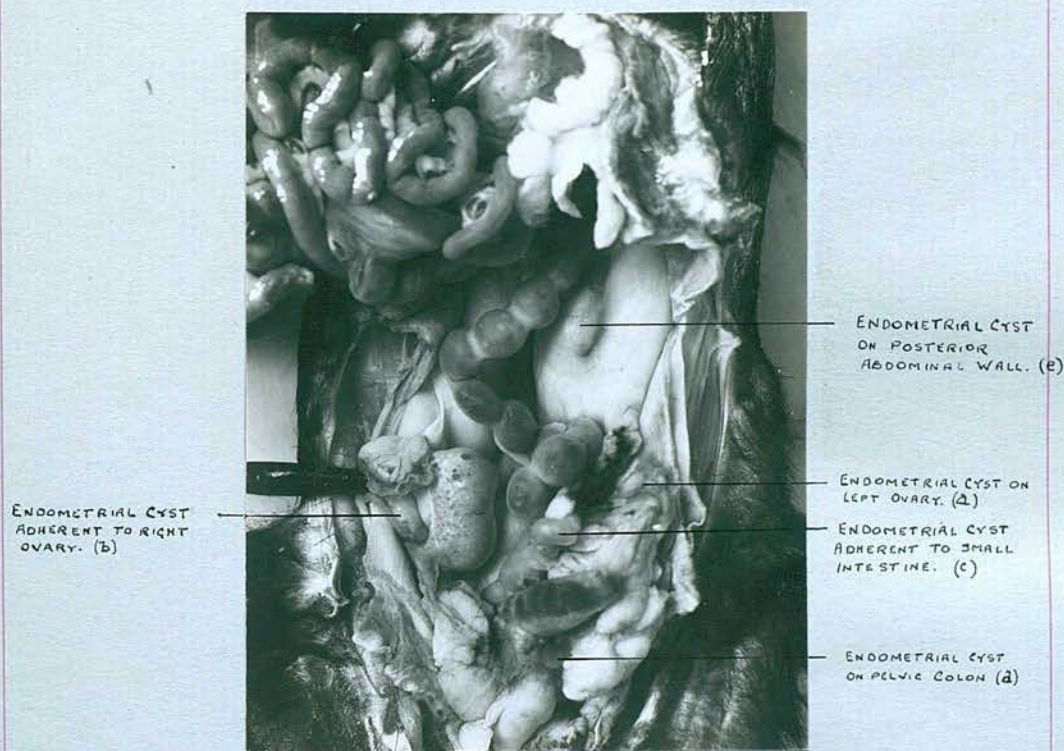
On incising the skin and exposing the aponeurosis covering the recti muscles two cystic swellings were found in the muscular layer and bulging under the rectus sheath (Fig. 41 a and b) in the position where the grafts had been inserted. The upper one (Fig. 41 - a) was thin walled, multilocular, and glistening with a clear fluid content. It measured  $\frac{1}{2}$ " across and was  $\frac{1}{2}$ " in thickness, and was firmly embedded in the muscular wall and fixed to adjoining tissues. The lower cyst (Fig. 41 - b) was approximately half the size of the upper one, was more mobile and was situated in the loose fascia covering the muscle.

On opening the abdomen a few adhesions were found between coats of intestines and the abdominal wall. Several thin walled cysts, varying in size from a pea to a small hazel nut, were seen studded about in the peritoneal cavity. One, about the size of a small nut, was found adherent to the left ovary posteriorly, adherent to rectum below and lightly adherent to the descending colon in front. It had a clear fluid content and several well defined bloodvessels could be seen running over the surface (Fig. 42-a).



Macroscopic appearance.

FIG. XLII. Endometrial cysts in abdominal cavity.



THE ABOVE PHOTOGRAPH TAKEN IMMEDIATELY AFTER THE ABDOMINAL CAVITY WAS OPENED POST MORTEM SHOWS SEVERAL ENDOMETRIAL CYSTS ADHERENT TO VISCERA IN THE LOWER PART OF THE ABDOMINAL CAVITY.

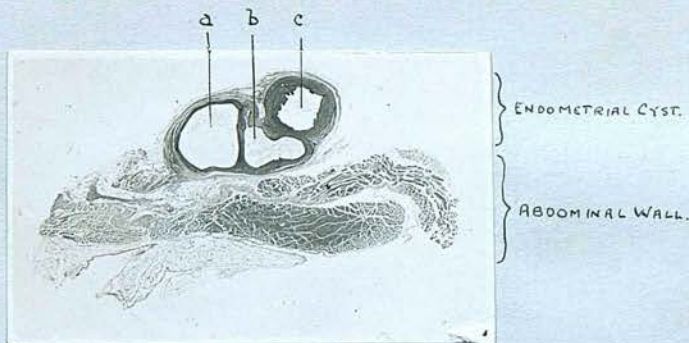


A similar cyst (Fig. 42-b) was found adherent to the right ovary, another adherent to a coil of small intestine (Fig. 42- c), and a smaller one was found growing on the anterior wall of the pelvic colon (Fig. 42 - d). The recto vaginal space was also found to contain a small multi-locular cyst adherent to the vagina anteriorly and the rectum posteriorly. One other was found in the posterior abdominal wall (Fig. 42 - e).

Microscopical appearances.

Endometrial Cyst in abdominal wall.

Low Power.      FIG. XLIII.



Microscopical examination shows a multi-locular cyst adenoma in the abdominal wall of exactly similar type to those obtained in the previous experiments. In two of the loculi (Fig. 43 - a and b) the epithelium is cuboidal and has almost disappeared - possibly the result of

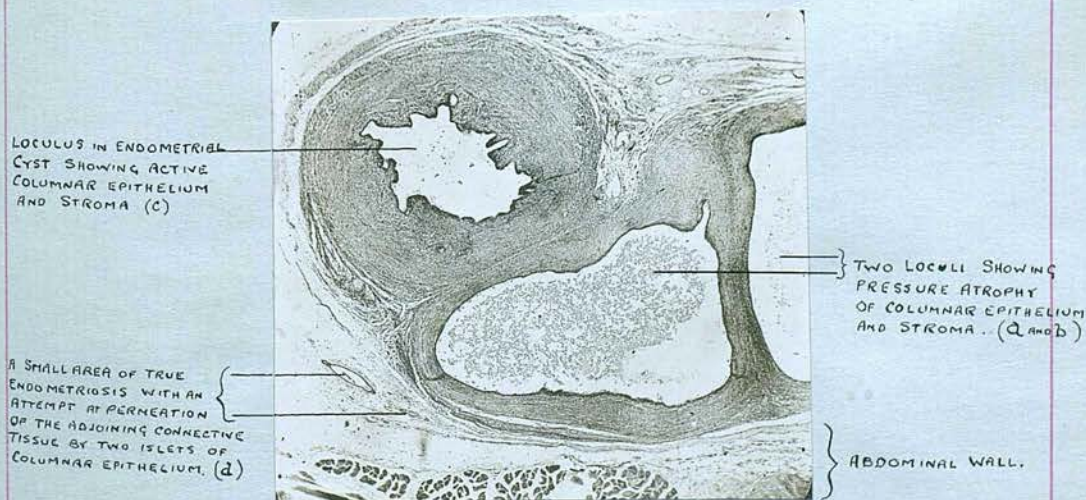


pressure atrophy, and the cyst wall consists almost entirely of fibrous tissue with little or no evidence of stroma. In one loculus, however, both columnar epithelium and stroma have preserved the normal appearance and show active growth (Fig. 43 - c). Probably this loculus is a fairly recent one and has, as yet, not lived for a sufficiently long period for intra cystic tension to have produced pressure atrophy.

There is little, if any, tendency for infiltration of the adjacent tissues by the endometrium except to a very slight degree (Fig. 44 - d), and unlike the early stages of endometrial implantation there is now no stroma or decidual like reaction in the adjoining connective tissue.

High Power.      FIG. XLIV.

Endometrial cyst in abdominal wall



This experiment proves conclusively that endometrium implanted in the abdominal wall will continue to grow and will produce a cystic tumour, the tissues of which maintain the characteristics of endometrium. It reproduces very closely that type of endometrioma found in the abdominal wall of the human female following such operations as Caesarean section and ventri suspension and described by Blair Bell, Bonney and many other writers. It strongly supports the theory that such endometriomata result from the accidental implantation of endometrium in the abdominal wall at the time of operation and it is the first of my experiments to reproduce fairly accurately one of the types of human endometriomata.

None of these experiments have shown to any marked degree that form of permeation of adjoining tissues by the endometrium which is such a distinctive feature in "endometriosis" in the human female. In order to try and produce some increased activity in the grafts it was decided that further experiments might be tried in order to investigate the possibility of increasing the cellular activity of the grafts by the introduction of new factors into the experiments. The first avenue to explore appeared to be the effect of endocrine influences on the grafts, so the following experiments were undertaken.



THE EFFECT OF ENDOCRINE INFLUENCES

ON ENDOMETRIAL GRAFTS.

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EXPERIMENT NO. VIII.

A fairly large black and white Angora rabbit of unknown age, but probably almost full grown, was used. With the routine technique the abdomen was opened and both ovaries and uterus were found to be rather small and in the quiescent stage. The right uterine cornu was resected and endometrium shaved off and cut into small pieces. One piece was fixed to the right ovary and one piece to the anterior surface of the pelvic colon by catgut stitches. The peritoneal cavity was then closed and the abdominal cavity of another female Angora rabbit was opened. The uterus of the second rabbit was large and congested from very recent or early pregnancy and both ovaries were large and contained corpora lutea. These ovaries were removed and were grafted into the abdominal wall of the first rabbit in order to provide additional ovarian hormone. The animal made an uninterrupted recovery but died sixty days later.

Post Mortem Examination-

At post mortem examination all the viscera in the abdominal cavity were found to be quite healthy. The lower ovary which had been grafted in the abdominal wall was found quite easily and it had become incorporated in the muscular layer. The upper grafted ovary was not found. In the

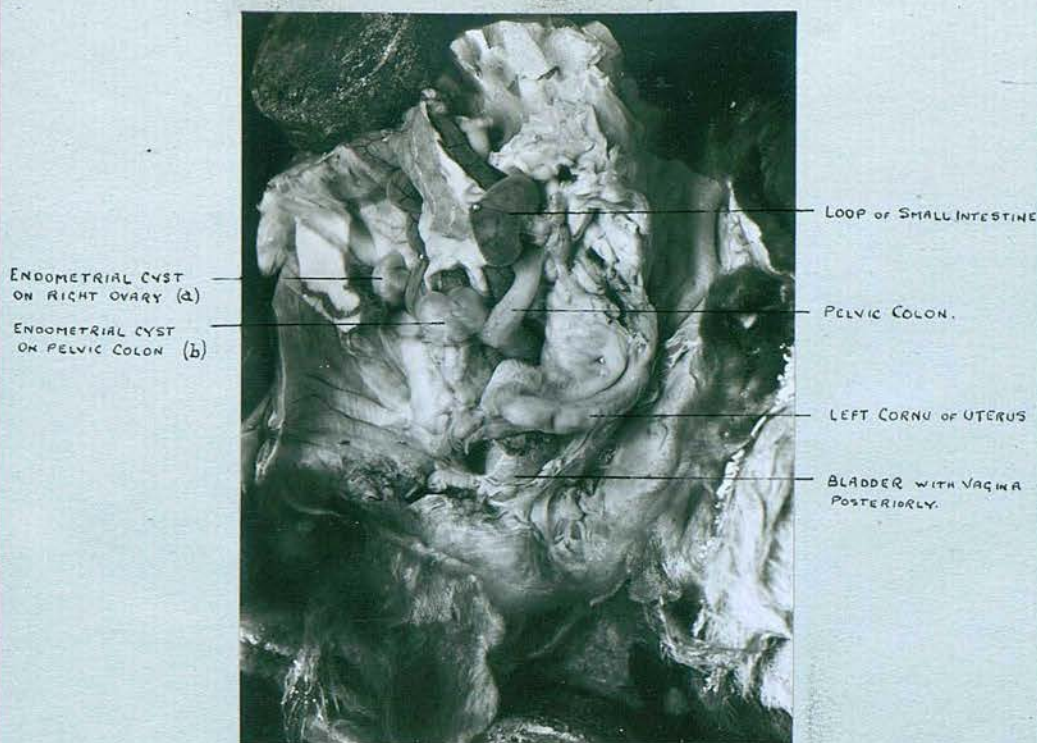
peritoneal cavity the endometrial grafts were at once apparent. Growing from the right ovary and also adherent to the posterior abdominal wall was a thin walled, translucent cyst almost the size of a hazel nut and firmly adherent to the ovary.

(Fig. 45- a). On the anterior surface of the pelvic colon where this second graft had been fixed was a large multilocular translucent cyst the size of a hazel nut adherent to the right side of the pelvic colon and adherent internally by fine adhesions to a loop of small intestine, and to the posterior abdominal wall. (Fig. 45 - b.) Many small adventitious blood vessels were seen running across the adhesions to the cyst. Both these cysts were very considerably larger than any previously obtained in these experiments and to the naked eye they appeared to exhibit much more active growth.



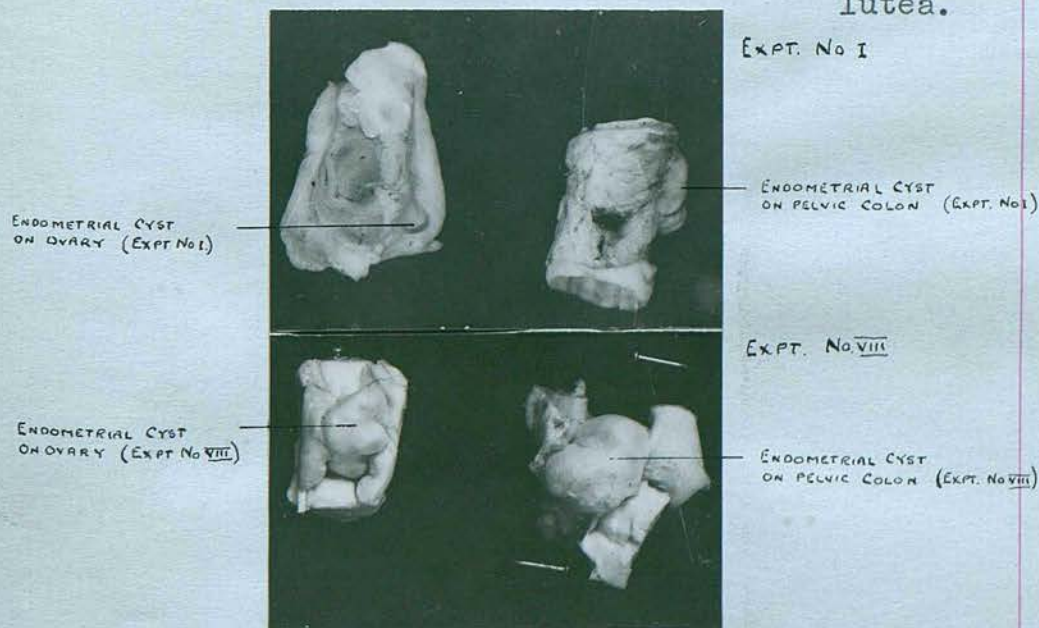
Macroscopic appearances.

FIG. XLV. Endometrial cysts in abdominal cavity after grafting accessory ovaries containing corpora lutea.



THE ABOVE PHOTOGRAPH SHOWS THE ABDOMINAL CAVITY POST MORTEM OF THE RABBIT IN EXPT. NO VIII. NOTE THE TWO LARGE ENDOMETRIAL CYSTS A AND B

FIG. XLVI. Comparison between simple endometrial cysts and those obtained by grafting accessory ovaries containing corpora lutea.



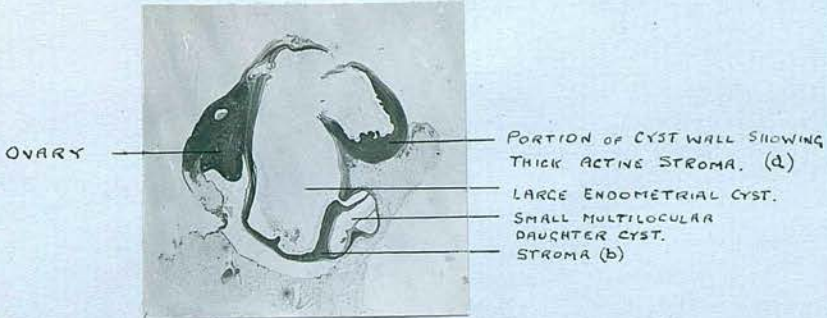
THE ABOVE PHOTOGRAPHS SHOW ENDOMETRIAL GRAFTS IN EXPT. NO I ABOVE AND IN NO VIII BELOW. THEY ARE SHOWN TOGETHER TO SHOW THE GREAT DIFFERENCE IN SIZE DUE TO THE ADDITIONAL OVARIAN HORMONE IN EXPT. NO VIII



FIG. XLVII.

Microscopic appearances.

Endometrial Cyst on right ovary.



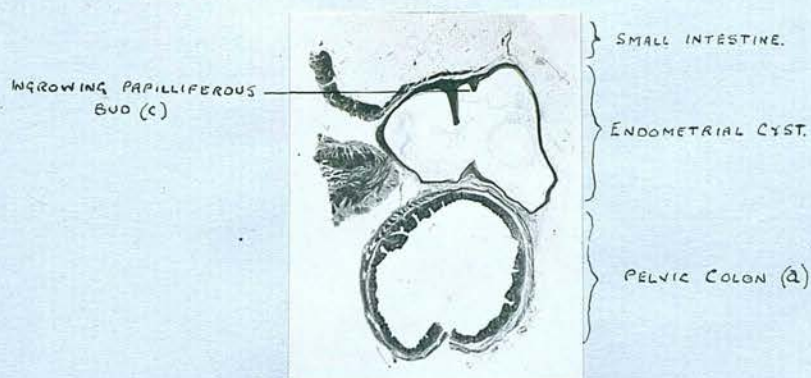
ABOVE IS SEEN A MULTILOCULAR ENDOMETRIAL CYST. OVARIES CONTAINING CORPORA LUTEA WERE GRAFTED AT THE SAME TIME. NOTE THE RELATIVE SIZE OF OVARY AND CYST. COMPARE EXPT. NO. I.

Here we see a multilocular cyst adenoma.

In some areas (Fig. 47 a. & b.) the cyst wall is composed of a thick layer of active stroma lined internally by active proliferating columnar epithelium which has been thrown into papilliferous projections. In other areas the cyst wall is thin, the stroma has practically disappeared and the endometrium is reduced to a thin layer of low cuboidal epithelium, obviously the result of pressure atrophy. Covering the whole cyst is a layer of fibrous connective tissue of varying thickness.



Fig. XLVIII. Endometrial Cyst on pelvic colon.



ENDOMETRIAL CYST AFTER  
GRAFTING ACCESSORY OVARIES  
CONTAINING CORPORA LUTEA.  
NOTE THAT THE CYST IS AS  
LARGE AS THE PELVIC COLON.  
COMPARE EXPT. NO I

In this case the endometrial cyst is very similar. Below it can be seen the adherent pelvic colon (Fig. 48 - a.) and a loop of small intestine is adherent to the upper surface. (Fig. 48 - b.) The cyst wall consists of a thin layer of connective tissue lined by low cuboidal epithelium but in places there is a thick layer of cellular stroma lined by active columnar epithelium. In two places very active ingrowing papilliferous buds are present (Fig. 48- c.)-



Fig. XLIX.

Papilloma in cyst wall.



Here we see an actively growing papillomatous ingrowth in the cyst wall. Both columnar epithelium and stroma show a very high degree of cellular activity, far greater than that seen in the previous experiments or even in the normal uterus, and this hyperactivity can only be attributed to the increased supply of ovarian hormone provided by the accessory ovaries.

So striking were the results obtained in this experiment in that a very marked increase in growth resulted in the grafts, due apparently to the additional supply of ovarian hormone, that it was resolved to repeat the experiment to see if similar results would again be obtained.

EXPERIMENT NO. IX.

For this experiment a fully grown black and white Angora rabbit and similar to the one in the last experiment was used. On opening the abdomen the viscera were all healthy and the uterus and ovaries were in the quiescent stage. The right uterine cornu was resected and the endometrium stripped off and divided into small pieces, one being stitched to the left ovary and one to a coil of large intestine. The remaining pieces, three in number, were scattered in the lower part of the abdominal cavity. The peritoneal cavity was closed and a second Angora rabbit, known to be pregnant, was anaesthetised and the abdomen opened. Both uterine cornua were enlarged by gestation sacs and both ovaries were enlarged and contained corpora lutea. The ovaries were removed and were grafted into the abdominal wall of the first rabbit, a pocket in each case being made under the rectus sheath and the ovaries being fixed to the rectus muscle by catgut ligatures.

The rabbit made a good recovery but fifty one days later was killed as it began to refuse its food.

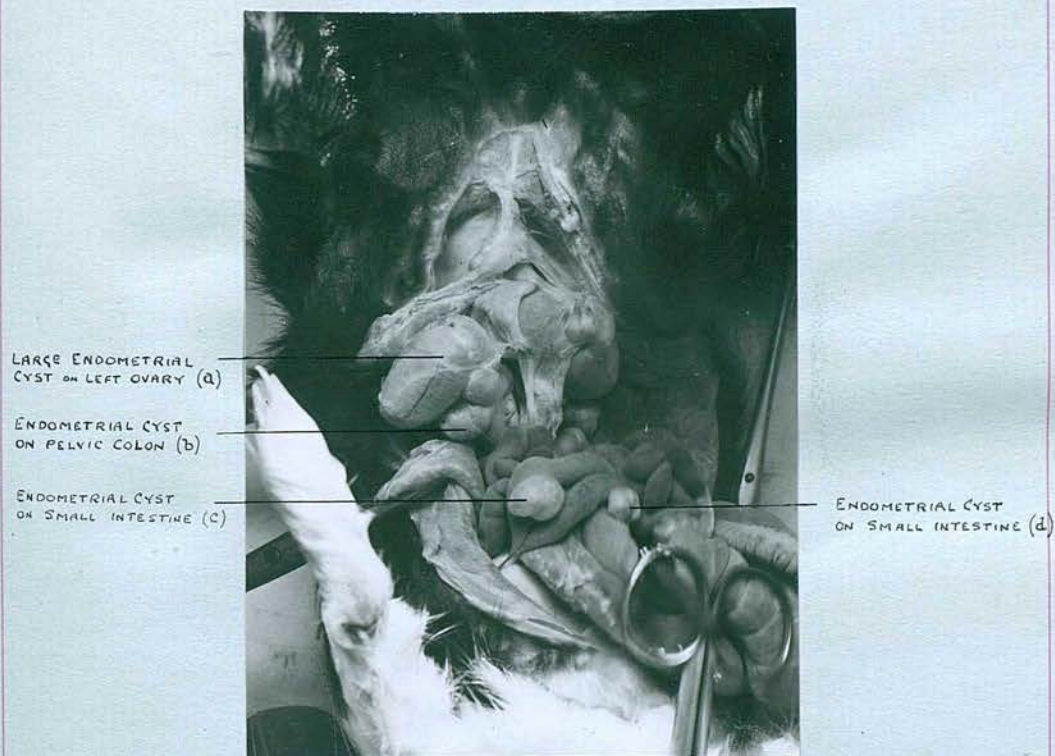
Post Mortem Examination.

When the skin was reflected both the grafted ovaries could be seen firmly embedded and incorporated with the rectus muscle. On opening the peritoneal cavity the endometrial grafts were at once apparent (Fig. 50 a. b. c. & d.). Growing from the left ovary was a large translucent thin walled cyst rather larger than a hazel nut and adherent posteriorly to small intestine and to the posterior abdominal wall (Fig. 50 - a.). Close to it was a similar though smaller cyst growing from the graft which had been fixed to the pelvic colon (Fig. 50 - b.) and adherent to the small intestine were two other similar cysts which must have originated from the loose grafts which had been put in the peritoneal cavity (Fig. 50- c. & d.). All these cysts were similar both in size and appearance to those of Experiment VIII, and were much larger than any obtained in previous experiments.



Macroscopic appearance.

FIG. L.      Endometrial cysts in abdominal cavity  
after grafting accessory ovaries  
containing corpora lutea.



THE ABOVE PHOTOGRAPH OF THE ABDOMINAL CAVITY OF THE RABBIT IN EXPT. NO. 9 WAS TAKEN IMMEDIATELY AFTER IT WAS OPENED POST MORTEM. FOUR LARGE ENDOMETRIAL CYSTS CAN BE SEEN. NOTE THE GLISTENING TRANSLUCENT APPEARANCE OF THE CYSTS, AND THE ADHESIONS TO THE ADJACENT VISCERA.



Macroscopic appearance

FIG. LI. Endometrial cyst on pelvic colon.

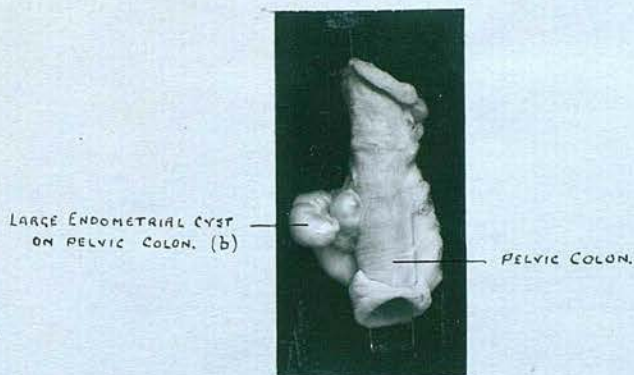


FIG. LII. Endometrial cyst on small intestine.

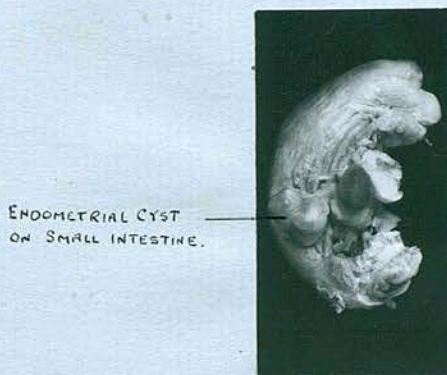
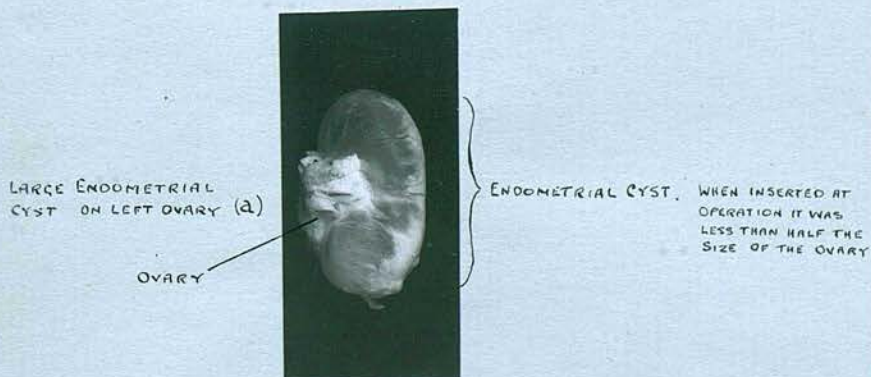


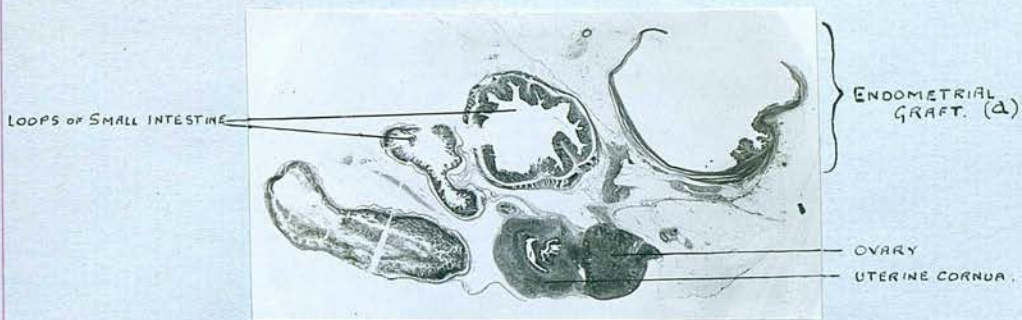
FIG. LIII. Endometrial cyst in ovary.





Microscopic Appearances.

Fig. LIV. Endometrial Cyst on left Ovary.



LARGE ENDOMETRIAL CYST. OVARIES CONTAINING CORPORA LUTEA WERE GRAFTED AT THE SAME TIME. NOTE THE LARGE SIZE OF THE CYST COMPARED WITH THE OVARY, AND COMPARE WITH EXPT I.

This specimen was removed together with the left ovary, an adherent loop of small intestine and part of the left uterine cornu. Fig. shows the endometrial cyst (a) though part of the cyst wall has become detached in preparation. It is similar in all respects to those seen in Experiment VIII and shows active growth in one area of the cyst lining and pressure atrophy in the remaining portion. The diameter of the cyst will be seen to be very much greater than that of the adjoining uterine cornu.



Fig. LV.

Endometrial Cyst on Pelvic Colon.



In this case the endometrial cyst has, formed many loculi and is adherent both to the pelvic colon and small intestine. Growth appears to have been exceptionally rapid, for not only are there many locuts but throughout the cyst the lining columnar epithelium has almost entirely disappeared as a result of pressure atrophy.

EXPERIMENT NO. X

Using the same technique as in the previous two Experiments a further experiment was performed. In this case two ovaries were removed from a non pregnant rabbit and were grafted in the abdominal wall simultaneously with the implantation of the endometrial grafts in the peritoneal cavity. The object of this experiment was to determine, if possible, whether the increased growth in the grafts observed in the two previous Experiments was due merely to the added ovarian secretion or to the additional hormone provided by the corpora lutea present in the ovaries employed. The rabbit was killed fifty five days later.

Post Mortem Examination.

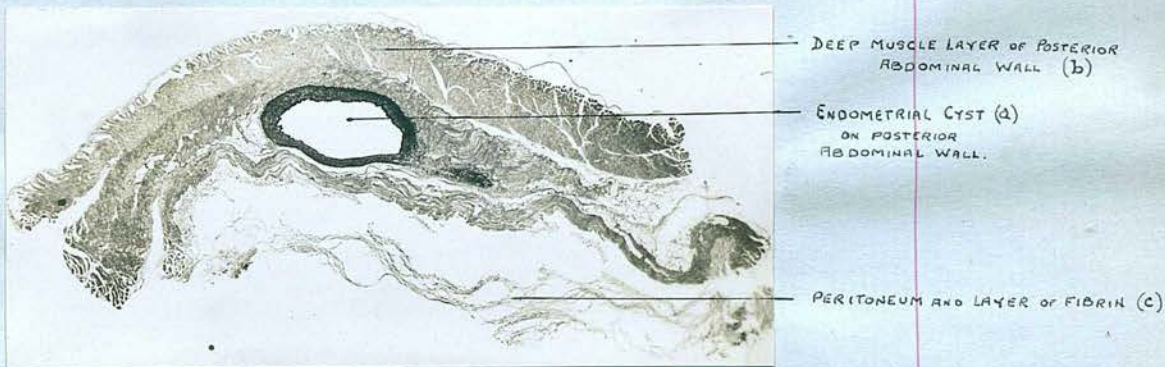
The two adventitious ovaries in the abdominal wall were located easily and both appeared to have established themselves for many small adventitious blood vessels could be seen running into them. On opening the peritoneal cavity several of the grafts were located but they were small in size and in no way comparable to those found in Experiments VIII and IX. They were little, if any larger than when inserted.



and the largest which was situated on the posterior pelvic wall was only 3 m.m. in diameter.

Microscopic Examination.

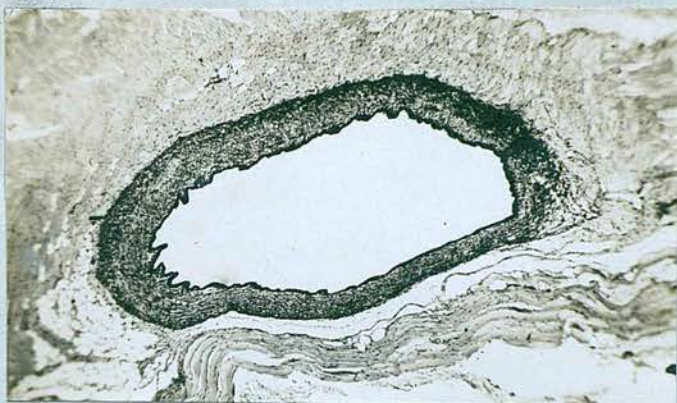
FIG. LVI. Graft on post abdominal wall.



Here we see a small endometrial cyst (a), partially buried in the muscular layer, (b), the surface being covered over by the serosa and by a layer of fibrin (c). It is similar in all respects to those already obtained previously in experiments where accessory ovaries were not used and does not show the markedly increased cellular activity so noticable when accessory ovaries containing corpora lutea were employed to increase the available ovarian hormone.



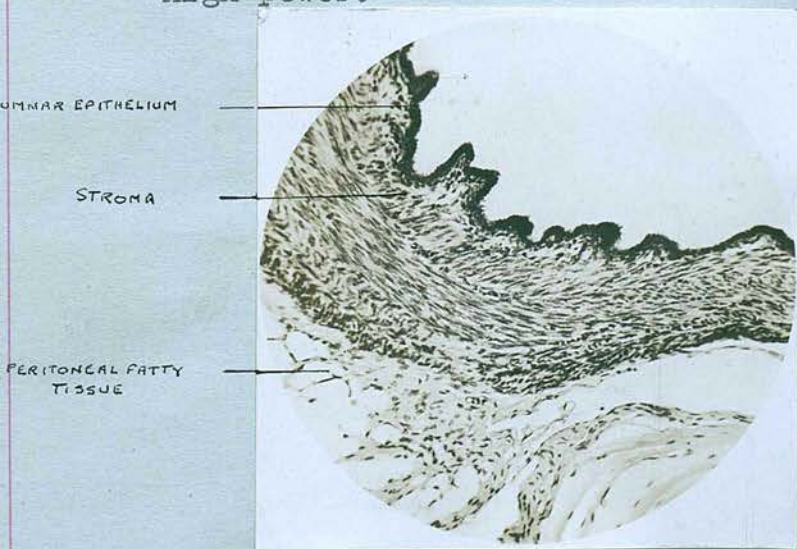
Fig. LVII. Endometrial graft on posterior abdominal wall.  
High power.



ENDOMETRIAL CYST ON POSTERIOR ABDOMINAL WALL. AT THE TIME THE GRAFT WAS IMPLANTED TWO OVARIES FROM A NON PREGNANT RABBIT WERE ALSO GRAFTED IN THE ABDOMINAL WALL.

Under higher magnification the endometrial tissue is seen to be very active though not unduly so. Both the columnar epithelium and stroma show active growth, but only comparable to that found in the majority of these Experiments, and there is no indication of any increased cellular activity resulting from the additional ovarian hormone.

FIG. LVIII. Portion of cyst wall.  
High power.



PORTION OF CYST WALL UNDER HIGHER MAGNIFICATION BOTH COLUMNAR EPITHELIUM AND STROMA SHOW ACTIVE GROWTH BUT NO MORE ACTIVE THAN IN PREVIOUS EXPERIMENTS IN WHICH ACCESSORY OVARIES WERE NOT USED. IN ACTUAL SIZE THIS CYST WAS SMALL

EXPERIMENT NO. XI.

The same technique as in the previous Experiment was again employed, grafts being scattered in the peritoneal cavity and two accessory ovaries from a non pregnant rabbit being embedded in the abdominal wall. Sixty days later the animal was killed and examined.

Post Mortem Examination.

Again both grafted ovaries were easily distinguishable and both appeared to have "taken". Only two grafts were recognisable in the peritoneal cavity, one projecting on the peritoneal surface of the anterior abdominal wall and one adherent to the posterior vaginal and anterior rectal wall. The former was about .5 cm in diameter and had a thin translucent wall, and the graft in the recto-vaginal septum seemed slightly smaller. They were very similar to those obtained in the previous experiment and did not show the exuberant growth so noticable in Experiments VIII and IX.



Microscopic Examination.

Graft on anterior abdominal wall.

Fig. LIX.



ANTERIOR ABDOMINAL WALL

ENDOMETRIAL CYST ON THE PERITONEAL SURFACE  
OF THE ABDOMINAL WALL.

ENDOMETRIAL CYST ON THE UNDER SURFACE OF THE ABDOMINAL WALL.  
AT THE SAME TIME THAT THE GRAFT WAS INSERTED TWO ACCESSORY  
OVARIES WERE ALSO GRAFTED INTO THE ABDOMINAL WALL.

Low power shows a unilocular endometrial cyst growing in the subperitoneal fatty layer of the abdominal wall. There is evidence of some pressure atrophy from increased intra-cystic tension for the columnar epithelium is very ill defined and in many areas the stroma has become compressed and inactive. Microscopically the cyst is somewhat similar to those obtained in the experiments where additional luteal hormone was supplied, but in actual size the cyst is in no way comparable.



Fig. LX. Graft on anterior abdominal wall

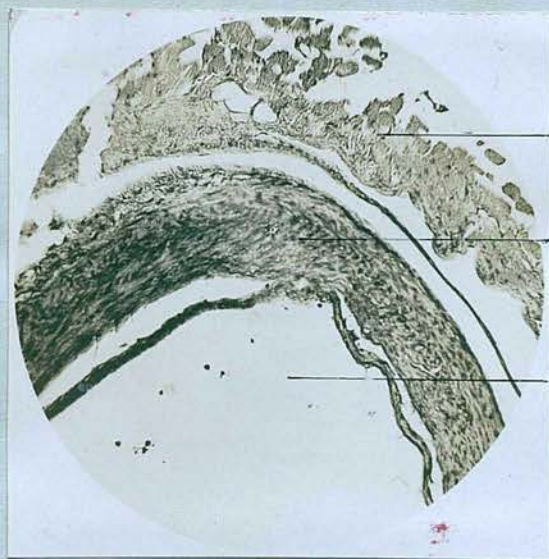


ABDOMINAL WALL

ENDOMETRIAL CYST

THE COLUMNAR EPITHELIAL LINING  
SHOWS SOME DEGREE OF PRESSURE ATROPHY  
DUE TO INTRA CYSTIC TENSION AND  
RAPID GROWTH.

Fig. LXI. High Power. Graft on abdominal wall



ABDOMINAL WALL

COMPRESSED STROMA,  
IN CYST WALL

ENDOMETRIAL CYST

Under higher power we see a fairly cellular cyst wall but almost devoid of any epithelial lining. There are no papillary projections in this cyst wall and no evidence of active growth, and again the picture is one of a much lesser degree of cellular activity as compared with the grafts in Experiments VIII and IX.

These four experiments, though somewhat in the nature of a digression from the strict confines of this work, are yet of some interest. The grafting of accessory ovaries containing corpora lutea from pregnant rabbits was prompted by the known association between lutein cysts and hydatidiform degeneration of the chorion, and even more constantly in the case of chorion epitheliomata. It was thought that it might be possible to produce proliferative change in the endometrial cysts by increasing the corpus luteum hormone.

The experiments show very definitely that the endometrium in a non pregnant animal is stimulated to proliferate greatly by the corpus luteum hormone. Experiments X and XI show just as definitely that the ovarian hormone which does not contain the corpus luteum hormone has practically no effect on endometrial growth. (43 & 44) Curiously enough Corner has found exactly the same thing while working along entirely different lines on pregnant rabbits. He concludes that the corpus luteum is an organ of internal secretion which has for one of its functions the production of a special state of the uterine mucosa which he calls progestational proliferation. These experiments, performed quite independantly, would appear to confirm fully Corner's conclusions.



The following two Experiments, though also a digression from the aim and scope of this work, are included as they may have some slight bearing on the influence of the endocrine secretions of the ovary on endometrial growths. In each Experiment endometrial grafts were transferred from a healthy female rabbit to the peritoneal cavity of a male rabbit, this having been suggested through an accidental laparotomy on a male rabbit. The results are not brought forward as being conclusive but are of some interest and may throw some light on the inter-relationship between the two constituents of the endometrium - the columnar epithelium and the stroma.

#### EXPERIMENT NO. XII.

The abdominal cavity of a rabbit, thought to be female, was opened in the usual way. It was then found that a mistake had been made and that it was male, so endometrium was removed from a female rabbit by the usual technique and transferred to the peritoneal cavity of the male. Two grafts were fixed by fine catgut ligatures to the posterior pelvic wall, one to the pelvic colon and the remainder, four in number - were scattered



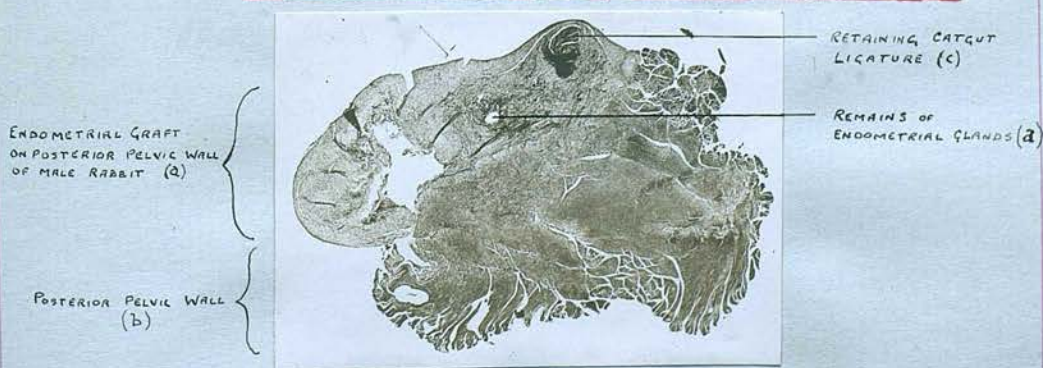
in the pelvic cavity. Thirty days later the animal was killed and examined post mortem.

### Post Mortem Examination.

On opening the peritoneal cavity no difficulty was experienced in locating the grafts. One was found where it had been fixed by ligature on the posterior pelvic wall, one that had been fixed to the pelvic colon was also adherent to the bladder anteriorly, and the third graft that had been stitched to the posterior pelvic wall had become detached and was adherent to some adjacent coils of small intestine. Two other grafts were found adherent to both the posterior bladder wall and anterior wall of the pelvic colon. All the grafts were rather whitish in colour, in sharp contrast to the deep red colour always found in female rabbits, all were rather smaller than when inserted and none were in the slightest degree cystic.

### Microscopic Examination.

FIG. LII. Endometrial graft on posterior pelvic wall of male rabbit.

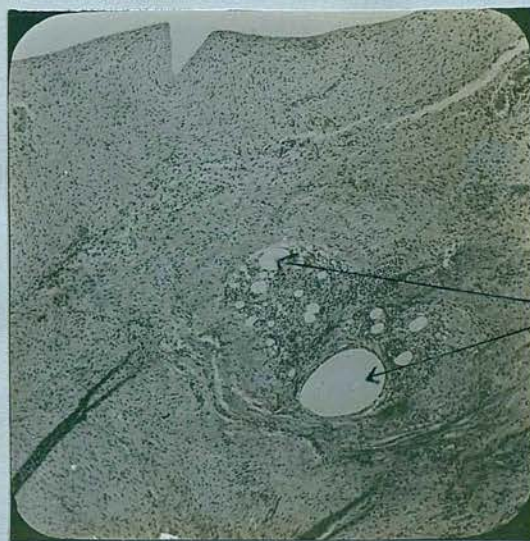




Here we see the graft (a) firmly adherent to the muscle of the posterior abdominal wall (b). At (c) can be seen the sites of the retaining catgut ligature. The graft is rather pale in colour and shows no vascular engorgement such as we have usually seen in the previous experiments. There is no attempt at cyst formation, in fact except at one small area (d) no glandular elements can be seen, and no columnar epithelium can be seen on the outer surface of the graft. The stroma is still fairly well defined.

FIG. LIII.

High Power.



STROMA OF ENDOMETRIAL GRAFT  
IN MALE RABBIT.  
NOTE AREAS OF COMMENCING  
HYALINE DEGENERATION.

REMAINS OF GLANDULAR SPACES (a)  
NOTE ABSENCE OF LINING  
COLUMNAR EPITHELIUM.

Under higher magnification - Fig.LIII the stroma of the grafted endometrium is seen to be alive and active, though paler areas of commencing hyaline change can be seen throughout. At (a) can be seen the remains of an epithelial islet but all the columnar epithelium has disappeared entirely and



merely the unlined acinar spaces remain. In a like manner the columnar epithelium has entirely disappeared from the surface of the graft.

Fig. LIV.

Graft from peritoneal surface of bladder.



ENDOMETRIAL GRAFT ON PERITONEAL SURFACE OF BLADDER  
IN A MALE RABBIT.

NOTE THE COMPLETE DISAPPEARANCE  
OF BOTH THE SURFACE AND DEEP  
COLUMNAR EPITHELIUM.

PERITONEAL SURFACE OF BLADDER.

In this section from another of the grafts the picture is the same. The stroma still persists and is fairly cellular, but the columnar epithelium has vanished and not even the gland spaces remain.

No definite conclusion can be drawn from this Experiment, but the fact that the stroma does survive and the columnar epithelium dies out entirely in a comparatively short time does suggest that the epithelial elements of the endometrium are much more dependant on the ovarian secretion than the stroma.



It was thought advisable to confirm the findings in this Experiment so a second one was performed.

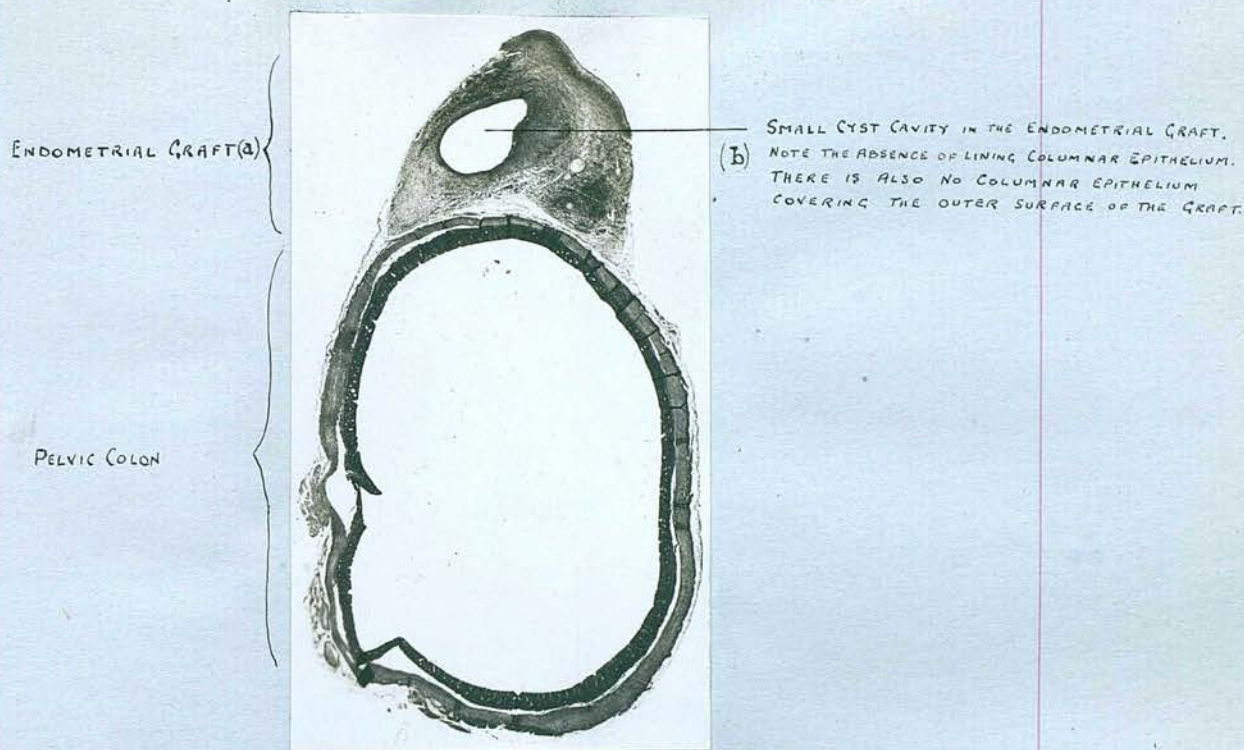
#### EXPERIMENT NO. XIII.

Endometrial grafts were procured from a mature female rabbit in the usual way. The peritoneal cavity of a fully grown male rabbit was then opened and two grafts were fixed by fine catgut ligatures, one to the anterior surface of the pelvic colon and one to the posterior pelvic wall. Two others were placed in the pelvic cavity loosely and the abdomen was closed. Thirty days later the rabbit was killed and examined post mortem.

#### Post Mortem Examination.

On opening the peritoneal cavity the grafts that had been fixed by ligatures were easily found. Both were rather pale in colour, firm and rather smaller in size than when inserted. The two loose grafts could not be found.

Fig. IV.      Graft on pelvic colon, of male  
rabbit.



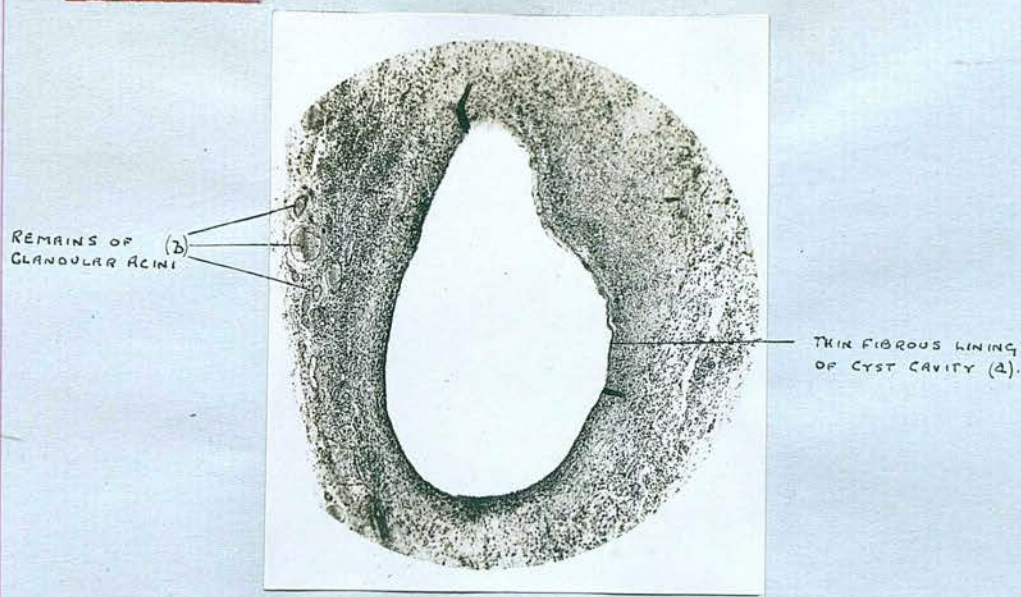
ENDOMETRIAL GRAFT ON PERITONEAL  
SURFACE OF PELVIC COLON IN A MALE  
RABBIT. THE STROMA PERSISTS BUT  
ALL THE COLUMNAR EPITHELIUM HAS  
DISAPPEARED. COMPARE WITH SIMILAR  
GRAFT IN FEMALE RABBIT IN EXPT. NO. 1.

The graft (a) can be seen firm implanted on the serosal surface of the pelvic colon. The stroma is well defined and cellular, but again no columnar epithelium remains. A fairly large cystic space (b) occupies the centre of the graft, apparently where an epithelial cyst had formed soon after implantation just as occurs in female rabbits, but the lining epithelium apparently disintegrated shortly afterwards and no trace remains.



FIG. LVI.      Graft on pelvic colon of male rabbit.

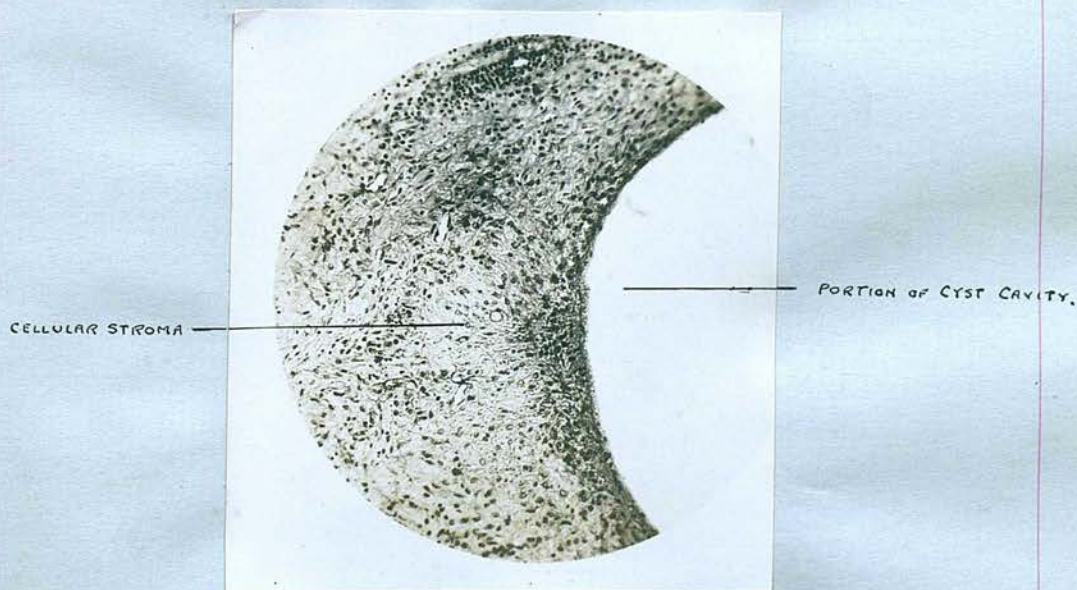
High Power.



CYST CAVITY IN AN ENDOMETRIAL GRAFT GROWN IN A MALE RABBIT. UNDER HIGH POWER THE CYST WALL IS SEEN TO BE LINED BY A THIN LAYER OF FIBROUS TISSUE. THERE IS NO COLUMNAR EPITHELIUM.

FIG. LVII.      Graft on pelvic colon of male rabbit.

Higher magnification.



ABOVE IS A PORTION OF THE GRAFT UNDER HIGHER MAGNIFICATION. ON THE RIGHT IS A PORTION OF THE CYST CAVITY ; TO THE LEFT IS TYPICAL STROMA ALL EPITHELIUM HAS DISAPPEARED





THE PRODUCTION OF SECONDARY IMPLANTATIONS  
FROM SIMPLE ENDOMETRIAL GRAFTS.

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These experiments have all shown that small pieces of normal endometrium when transferred to sites away from the Uterus in the same animal will continue to grow there, or if scattered free in the peritoneal cavity will often anchor themselves and then form small cystic growths. Sampson, in his theory, maintains that a similar process occurs in the human female, that retrograde menstruation implants fragments of endometrium on the ovaries resulting in the formation of "tarry ovarian cysts" and that subsequent rupture of these cysts lead to widespread dissemination of the endometrial tissue with the production later of diffuse pelvic endometriosis. It occurred to me that one might test the possibility of producing secondary growths from the primary growth experimentally and with this in view the following experiments were performed.



EXPERIMENT NO. XIV.

A fully grown Angora rabbit was used for this experiment. Adopting the same technique as in previous experiments the left uterine cornu was resected and two large pieces of endometrium were shaved off. One piece was fixed to the posterior pelvic wall by a retaining catgut ligature, and the second was similarly implanted in the recto vaginal space. The abdominal wound was closed and the animal made a good recovery.

Ninety days later, under ether anaesthesia, the abdomen was again opened. The abdominal scar was found to be well healed and the peritoneal cavity and pelvic viscera appeared healthy. There was an adhesion between a loop of small intestine and the stump of the left uterine cornu. The graft on the posterior pelvic wall was easily found and it had formed a small thin walled cystic swelling of the type seen in previous experiments, measuring about .25 c.m. in diameter. It was removed and an attempt was made to excise a portion of the cyst wall for re-implantation but owing to its small size the procedure was found to be impossible. The graft in the recto vaginal space had formed a larger cyst of about .5 c.m. in diameter

and it was an easy matter to excise a portion of the cyst wall. This excised portion was then buried in a stab wound in the right ovary and retained there by two covering catgut ligatures. The animal was then allowed to recover.

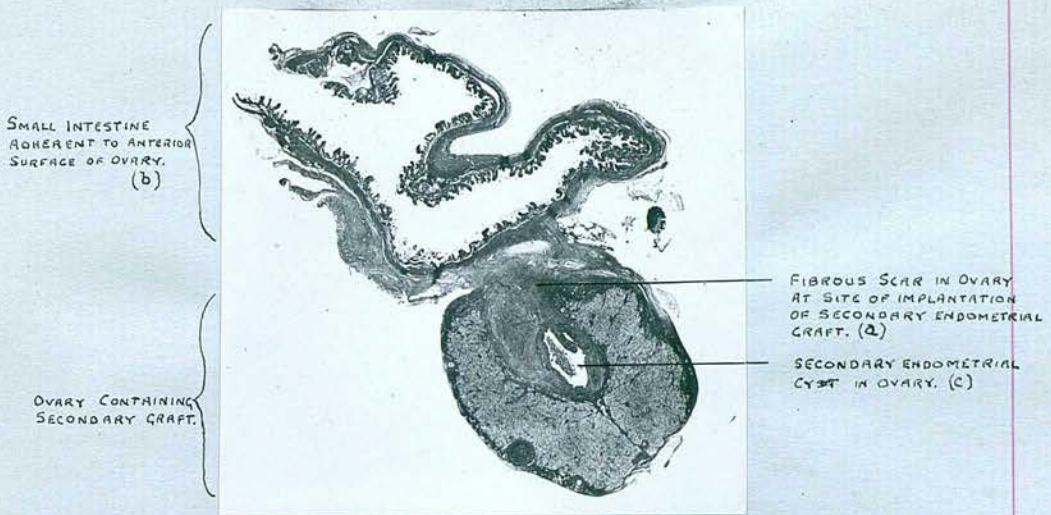
Four months later (121 days) it was killed and a post mortem examination was made.

On opening the abdomen rather widespread adhesions were encountered. Several loops of intestine were adherent to the posterior pelvic wall at the site of excision of the primary graft, and the right ovary in which the secondary graft had been implanted was hidden by two loops of small intestine adherent to the point of implantation. There was no sign of the secondary graft on naked eye inspection so the ovary with adherent intestine were removed carefully for microscopic examination in serial sections.

Microscopic Examination

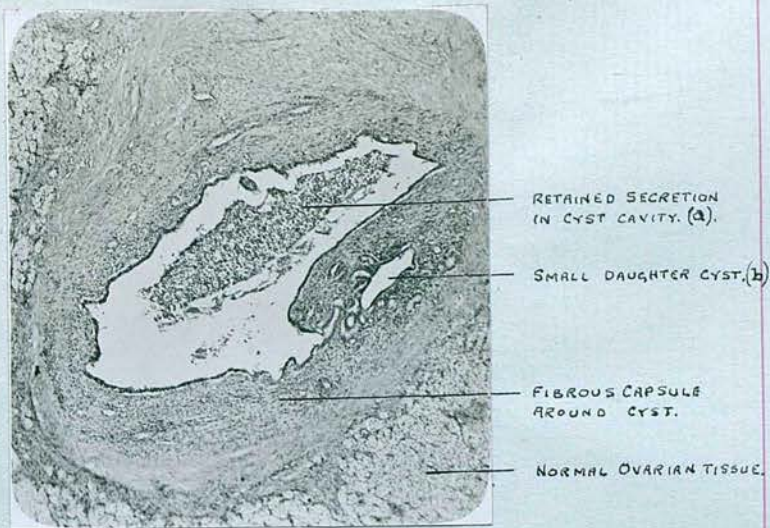
Fig. LIX.

Secondary endometrial  
graft in right ovary



Above we see a section taken through the centre of the ovary and through an adherent loop of small intestine. The scar in the ovary at the point of implantation (a) can be seen to which a loop of intestine is adherent (b). In the centre of the ovary is a small cystic space (c) with some secretion in the cavity and surrounded by an area of fibrous tissue.



Secondary endometrial graft in ovary.Fig. LX. High Power.

Higher magnification shows a small cavity in the centre of the ovary lined by low cuboidal epithelium and containing some secretion which appears to have shrunk during fixation (a). At one point (b) there is evidence of glandular proliferation with the production of a small daughter cyst. Surrounding the cyst cavity is a rather dense layer of fibrous tissue though in immediate proximity to it is a slight suggestion of an enveloping stroma but the cytogenous mantle of stroma is less marked than in the case of primary cysts.

It would appear from this experiment that secondary implantation from an endometrial cyst is quite possible but it was considered advisable to confirm this by further experiment.

EXPERIMENT NO. XV.

Using the same technique as in the previous experiment primary endometrial grafts were implanted on the posterior pelvic wall and in the recto vaginal space. Eighty six days later laparotomy under ether anaesthesia was performed. The site of the graft on the posterior pelvic wall was covered over by adherent pelvic colon and the graft could not be exposed without danger to the animal. In the recto vaginal space was a small cyst at the site of implantation of the graft, again about .5 c.m. in diameter and with rather thicker and more vascular walls than usual in these transplants. A portion of the cyst wall, approximating one-third, was removed, and this piece was fixed to the anterior aspect of the pelvic colon by a retaining catgut ligature about 3" above the primary graft. The abdomen was closed.

Forty five days later the animal became ill so was killed, and a post mortem examination was made.

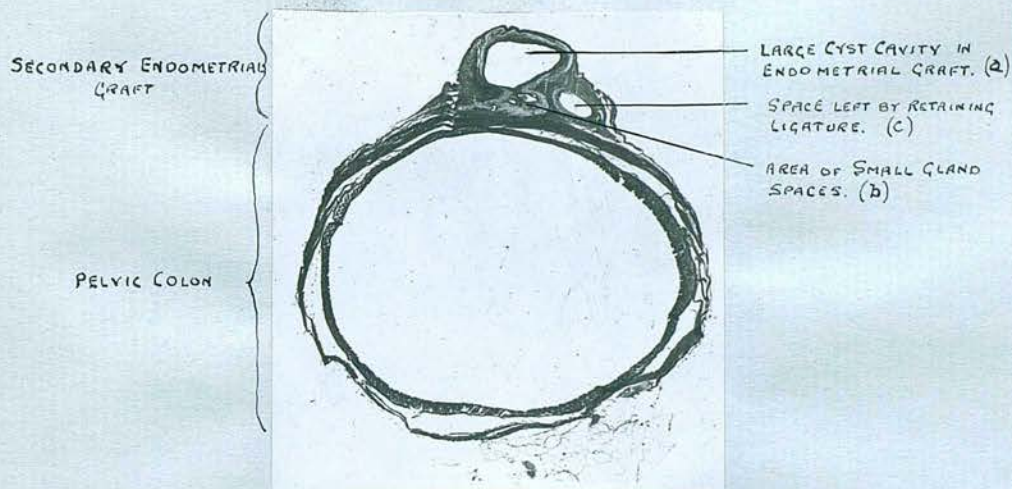
Post Mortem Examination.

On opening the abdominal cavity no gross abnormality could be discovered to account for the illness. The secondary graft was easily found and was seen as a small pink nodule projecting on the anterior wall of the pelvic colon. There were no adhesions around it. The recto vaginal septum had become closed over by adhesions but on cutting into these the primary graft was found. It was rather smaller than at the previous operation but the excised portion appeared either to have closed in or to have become covered over by adherent rectum.



Microscopic Examination.

Fig. IXI.      Secondary endometrial graft  
on pelvic colon.

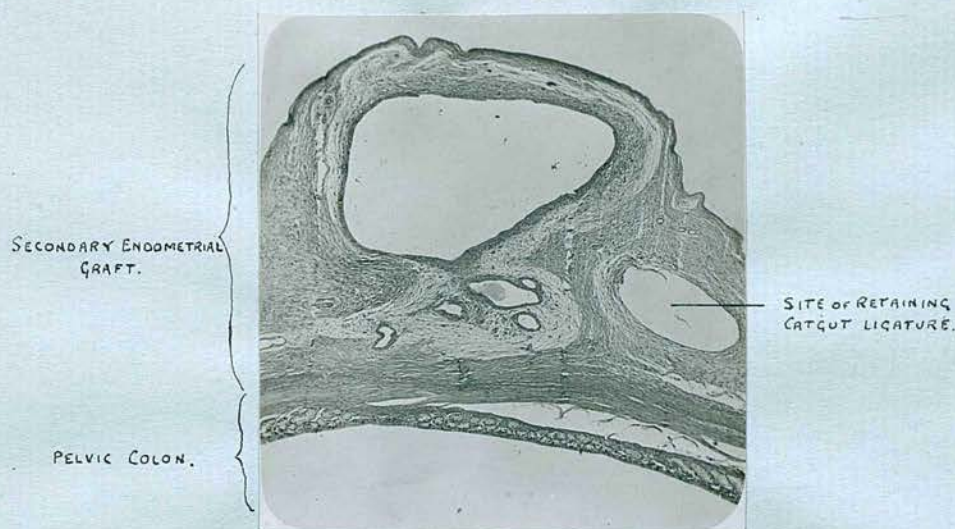


The secondary graft can be seen forming a small rather thick walled cyst on the peritoneal surface of the pelvic colon. There is one large cyst cavity (a) but there are several small glandular areas between it and the lumen of the bowel. (b). At (c) can be seen the space left by removal of the retaining catgut ligature.



Fig. LXII. High Power.

Secondary endometrial graft on pelvic colon.



The larger cyst cavity is seen to be lined with low cuboidal epithelium and the small glandular areas by tall active columnar epithelium. There is a good deal of fibrous tissue around the graft, but it presents all the characteristics of and is indistinguishable from the primary endometrial implants.

These two experiments show that a secondary implantation in the same animal from primary endometrial transplants can be successfully performed experimentally. It tends to confirm Sampson's view that widespread dissemination of endometrial tissue may occur from a primary focus of aberrant endometrium.

OBSERVATIONS ON THE BEHAVIOUR OF  
AUTOGENOUS SEROSAL IMPLANTS.

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Having in all these experiments failed by transplantation of endometrium to reproduce the true features of diffuse endometriomata at all accurately it occurred to me that experiments might be performed to test the theory first advanced by Iwanoff and supported by Robert Meyer and now held to be correct by many observers that the gland spaces in adenomyomata are derived from downgrowths of the serosal epithelium and that they are peritoneal in origin. According to Meyer the transition from endothelium to epithelium is an expression of "surface expansion", though Klage, who investigated the subject very thoroughly, considered it to be the result of inflammatory irritation. The supporters of this "serosal" theory maintain that in response to some external stimulus - possibly inflammation - the flat endothelium of the peritoneum becomes first of all cuboidal in type and later may even assume the columnar form. They maintain that the stimulus which causes it to change in type also activates this epithelium to form downgrowths into the subjacent connective tissue and so the diffuse form of adenomyoma may commence.

It appeared to me to be a line of experimental work which not having been previously investigated by other workers, might throw some light on the correctness or otherwise of the "serosal" theory.

EXPERIMENT NO. XVI.

For this experiment a large fully grown female Angora rabbit was used. The abdomen was opened and all the viscera found to be healthy. A portion of the serous coat of the uterus was shaved off each uterine cornu and portions of the serosa then obtained were used as serosal implants. One piece was embedded in a stab wound in the left ovary and was retained there by catgut ligatures. The peritoneal surface of the pelvic colon was then incised and a flap of peritoneum was then gently lifted up; beneath this a portion of the uterine serous coat was inserted and the flap of peritoneum was stitched over. In the same way a serosal graft was buried in the posterior vaginal wall and the rectum was fixed over it by catgut ligatures. The abdomen was then closed.

Thirty days later the rabbit was killed and examined post mortem.

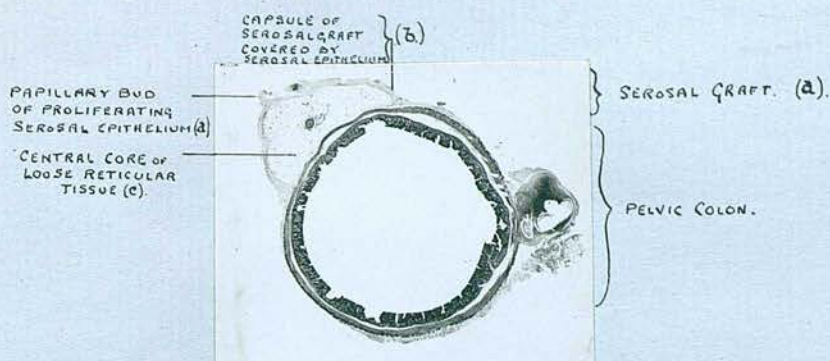
Post Mortem Examination.

On opening the abdomen all the organs appeared healthy and the raw areas on the uterine cornua where the serous coat had been stripped off had healed over leaving a whitish scar in each case. There were some fine adhesions around the left ovary and the site of the stab wound was easily apparent as the catgut ligature was still in situ and not yet absorbed. Over the stab wound was a small translucent nodule which appeared solid and quite unlike the endometrial cysts found in previous experiments. The ovary was removed carefully for examination. On the surface of the pelvic colon was a similar small translucent apparently solid nodule and it could be identified as the serosal graft by the retaining catgut ligature which was still present. In the recto-vaginal septum the posterior vaginal wall and anterior rectal wall could be seen to be adherent, though between them was a small solid whitish nodule rather similar to the one seen on the pelvic colon. These specimens were removed for examination.



# Microscopic Examination.

FIG. LXIII. Serosal implant on pelvic colon.

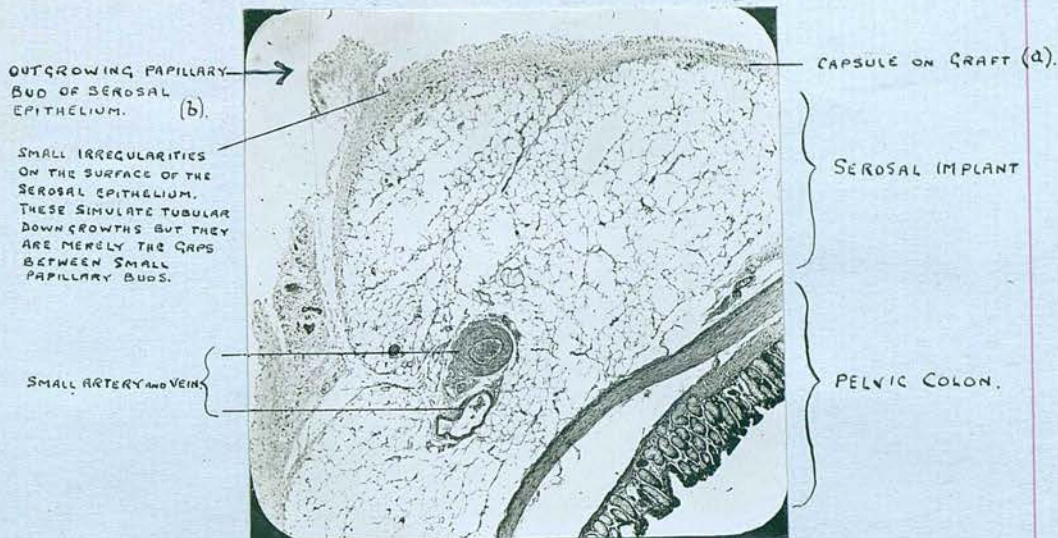


THE ABOVE FIGURE SHOWS THE SEROSAL GRAFT GROWING ON THE SURFACE OF THE PELVIC COLON. BELOW AND TO THE RIGHT IS THE UPPER PORTION OF A SECOND GRAFT IN THE RECTO VAGINAL SEPTUM.

Under low power a distinct nodule can be seen on the peritoneal surface of the pelvic colon (Fig. 63- a.). It appears to have a thin and definite capsule of compact tissue (Fig. 63- b.), with a central core of loose reticular tissue (Fig. 63- c.) and the whole graft appears to have grown firmly on to the colon. At either extremity of the graft the capsule merges into the peritoneal covering of the bowel below which the graft was inserted and on the most prominent portion of the graft there is a small projection (Fig. 63- d.) which appears to be an actively growing papillary bud. There is no evidence of any tendency for the tissues of the graft to invade the intestinal wall and the growth appears to be purely on the surface.



Fig.LXIV. High Power. Serosal implant on pelvic colon.



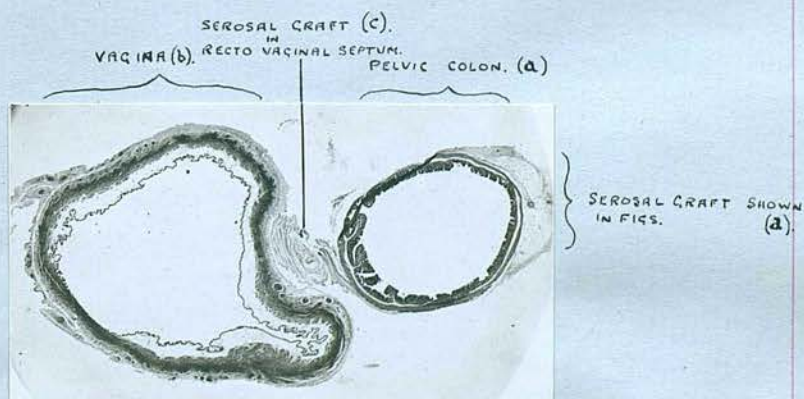
Under high power the structure of the serosal graft can be seen in more detail. The capsule is seen to consist of a layer of very fine cellular connective tissue (Fig.64 - a.) - in all probability derived from the sub serous layer portions of which must have been implanted with the graft - with a covering of thin serosal epithelium one or two cells thick. This serosal epithelium appears to be growing actively for the surface is slightly irregular and has been thrown into folds and at one point there is a well defined papillary bud (Fig.64 - b.). The surface of this serosal epithelium is somewhat irregular and here and there would appear to show small tubular downgrowths similar to those described by Klage in support of



the serosal hypothesis. Careful observation shows, however, that they are most decidedly not tubular downgrowths but merely irregularities on the surface resulting from rapid growth of the serosal epithelium, for on the papillary bud the same effect is produced in between the small papillary projections. The tendency appears to be for the serosal epithelium to grow outwards from the surface and there is no evidence whatever of any tendency for downward infiltrative growth. The central portion of the serosal implant is seen to consist of very loose reticular tissue and in the centre a small artery and vein can be seen which must have been included in the graft during fixation.

Fig.LXV. Serosal implant in recto - vaginal septum.

Low Power.



ON THE LEFT IS THE VAGINA AND TO THE RIGHT IS THE RECTUM  
BETWEEN THEM IN THE RECTO-VAGINAL SEPTUM IS THE  
SEROSAL GRAFT. ON THE EXTREME RIGHT AND GROWING  
DOWN ONTO THE RECTUM IS THE FIRST SEROSAL GRAFT.



Fig. 65 shows the rectum (a) and vagina (b) with the serosal graft between them and adherent to both (c). On that side of the pelvic colon distant from the vagina portions of the other serosal graft shown in Fig. 63 can be seen (d) for it has extended down the pelvic colon to the level of the second graft. The serosal graft has formed a small solid nodule adherent to the rectum and vagina but with no evidence of infiltration of either.

High Power.

FIG. LXVI. Serosal implant in recto-vaginal septum.



THE ABOVE IS A HIGH POWER PHOTOGRAPH OF THE SEROSAL GRAFT IN THE RECTO VAGINAL SEPTUM. NOTE THE COMPLETE ABSENCE OF ANY TENDENCY FOR THE SEROSA TO INFILTRATE ADJACENT TISSUES. NOTE ESPECIALLY THE TENDENCY FOR THE SEROSAL EPITHELIUM TO FORCE A WAY OUT TOWARDS THE SURFACE

Under high power the structure and mode of growth of this serosal implant are well shown, and are similar in many respects to those in the previous specimen. The central core is composed of a fine cellular connective tissue derived from the sub serosa implanted with the graft and the serosal epithelium lines the surface. At each side of the graft the serosal epithelium is seen to be growing rapidly and to have formed numerous active papillary buds and it gives the impression that it is making a vigorous attempt to grow out on to the free surface rather than any attempt at infiltration of either vaginal wall or rectum. As will be seen in later sections this serosal epithelium always forces its way to the surface of any organ in which it is buried. Not only does it make no attempt to infiltrate structures in which it is embedded but it would appear incapable of remaining alive when completely shut off from the surface.



Fig. LXVII. Serosal Graft in Ovary.

Low Power.

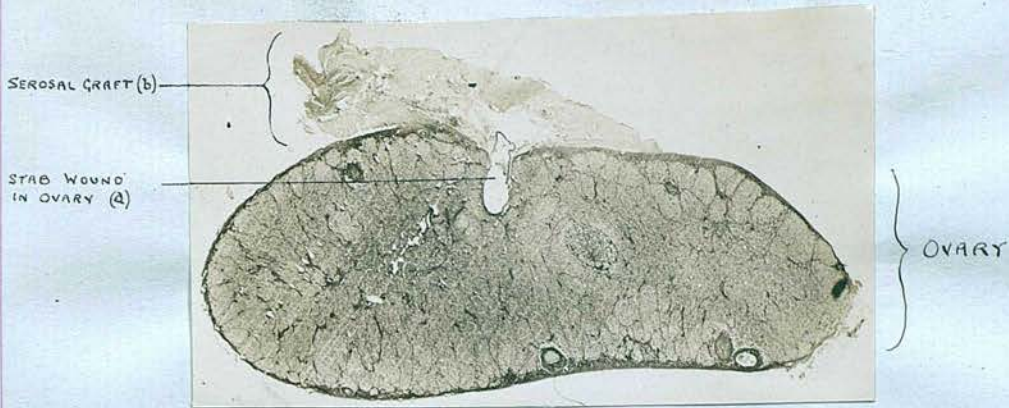


Fig. 67 shows a section of the ovary in which a serosal graft was embedded in a stab wound. The major portion of the ovary is seen to be normal and on one point on the surface the serosal graft is clearly apparent, the features exhibited in the previous grafts being even more pronounced. The stab wound (Fig. 67 - a.) can be seen as a cavity extending from the surface well down into the ovarian substance and it has become lined with a protective lining of fibrous and connective tissue. The serosal graft (Fig. 67 - b.) is still growing actively but has left the recess in which it was embedded and appears to have forced its way out on to the surface. Again we see this



inability of the serosa to maintain itself beneath the surface and its determination to survive by reverting to its normal site. The serosal epithelium can be seen lining the surface of the graft but has not survived in the stab wound nor does it appear to have formed a lining for this cavity as in the case with endometrial grafts. At no point is there any evidence of a transitional process into columnar epithelium or of any tendency for this peritoneal epithelium to become invasive, in fact the experiment strongly points to a complete inability for it to be other than a surface covering.

Fig.LXVIII. High Power.

Serosal implant in ovary.

ACTIVELY GROWING  
BUDS OF SEROSAL  
EPITHELIUM



SEROSAL GRAFT.

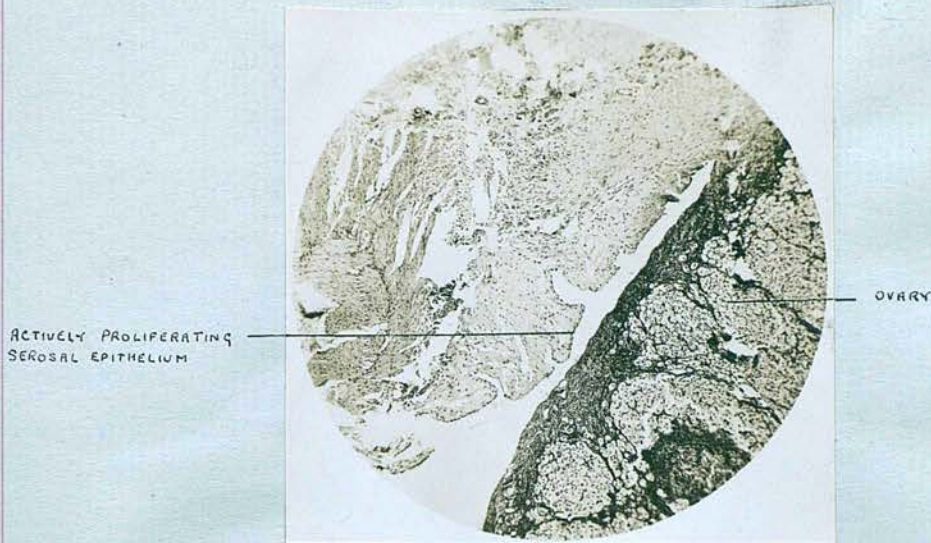
CAVITY IN OVARY  
PRODUCED BY  
STAB WOUND

THE ABOVE PHOTOGRAPH SHOWS THE OVARY WITH THE SEROSAL GRAFT ON THE SURFACE. THE STAB WOUND CAN BE SEEN AS A CAVITY WITH A LINING OF FIBROUS TISSUE. THE SEROSAL GRAFT HAS FORCED ITS WAY OUT OF THE STAB WOUND ON TO THE SURFACE AND NONE REMAINS BENEATH THE SURFACE, THOUGH IT STILL EXHIBITS ACTIVE PROLIFERATION SUPERFICIALLY.



FIG. LXIX. Serosal implant in ovary.

Higher magnification.



THE ABOVE PHOTOGRAPH WITH HIGH MAGNIFICATION SHOWS  
THE SEROSAL GRAFT GROWING ACTIVELY AFTER IT HAS  
FORCED ITS WAY TO THE SURFACE. THE ACTIVELY GROWING  
PAPILLAE LEAVE SPACES WHICH SIMULATE TUBULAR  
DOWN GROWTHS.

EXPERIMENT NO. XVII.

In order to confirm the negative result obtained in the previous experiment, by transplantation of serosal epithelium, it was decided to perform a somewhat similar one and to observe the results.

Using exactly the same technique the serosal coat was removed from the posterior surface of one uterine cornu and was divided into two pieces. One was embedded in a stab wound in the right ovary and the second graft was embedded in the anterior surface of the right lobe of the liver and the abdomen was closed.

Fifteen days later the animal died and a post mortem examination was made.

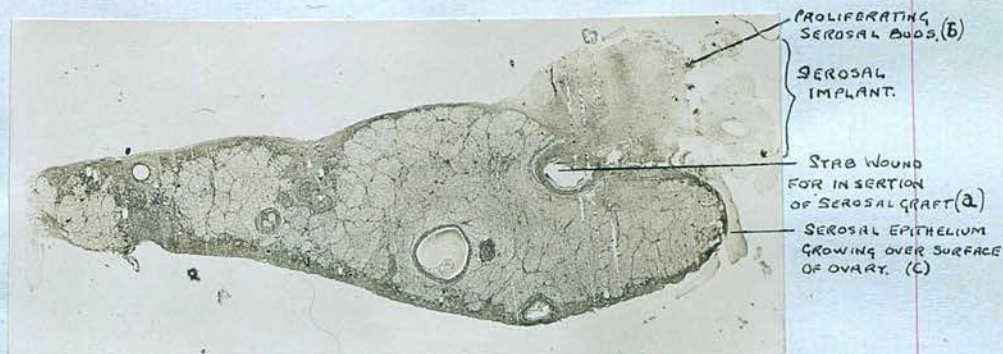
Post Mortem Examination.

The cause of death was not apparent and all the abdominal viscera seemed healthy. The stab wound in the right ovary was still recognisable and bulging from it was a small whitist translucent nodule similar to those found in the previous experiment. The stab wound in the liver appeared



as a pale linear scar and bulging from it was a small whitish projection similar to that found in the ovary. Both ovary and the portion of liver were removed for microscopic examination.

Fig. LXX. Serosal Graft in right Ovary.



The picture here is almost identical with that of the previous experiment. The stab wound, which has become much smaller than when made at the experiment, is seen as a distinct recess on the surface of the ovary (Fig. 70 - a.) which has acquired a lining of fibrous tissue. The serosal graft has not remained below the surface but has burst from the cavity and can be seen as a large nodule spreading over the surface of the ovary. None of the graft has remained buried but active epithelial proliferation can be seen in a few areas on its outer exposed surface (Fig. 70- b.). At the edges of the graft there is a distinct tendency displayed by the serosa to spread over the outer surface of the ovary (Fig. 70- c.).



FIG. LXXI. Serosal implant in ovary.

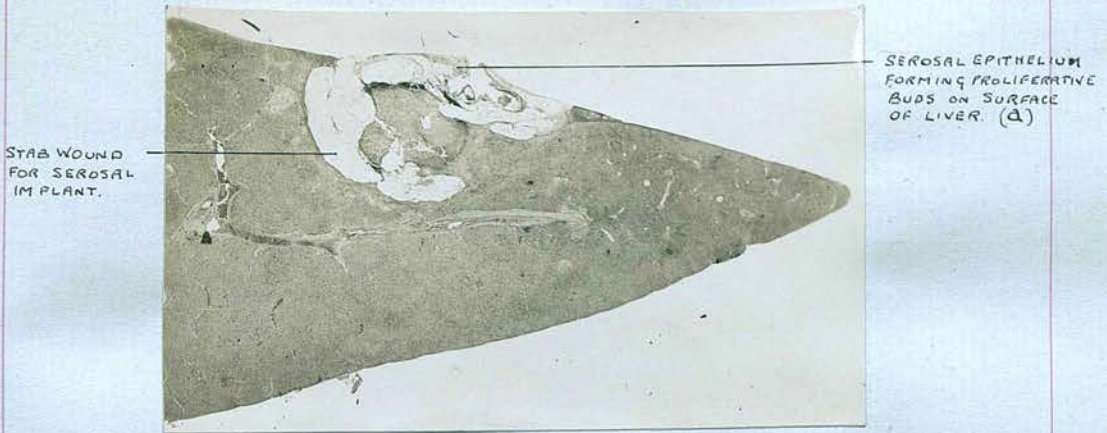
High Power.



Under high power it is apparent that none of the graft has remained alive below the surface. It gives the impression of having forced its way out to the exterior where it continues to exhibit a certain degree of cellular activity. The major portion of the central area of the graft has undergone hyalin degeneration all cell definition being lost, and only on the external aspect is the surviving serosal epithelium evident. This serosal epithelium exhibits active growth at several points on the outer surface of the graft (Fig. 71 - a) which in places has reached such a degree of activity as to produce epithelial buds.



Fig. LXXII.     Serosal Graft in Liver.



In the liver precisely the same condition is found. The stab wound is distinctly shown but none of the serosal graft has remained in it but it has forced a way to the surface where a few areas show some degree of epithelial regeneration. (Fig. 72 - a.).



FIG. LXXIII. Serosal implant in liver.

High Power.



With higher magnification the stab wound in the liver is seen to have become lined with fibrous tissue. None of the serosa appears to have remained in it, but there is some regeneration of serosal epithelium where the graft has forced a way to the exterior and here several well defined epithelial buds are evident (Fig. 73 - a.).

No confirmation of the serosal theory for the production of adenomyomata is obtained from these experiments. These experiments show that the serosal epithelium can only live on an external surface. If buried beneath the surface it will force its way back to the surface and there continue to live, but if it remains buried it appears to be unable to survive and rapidly to die.



THE INFLUENCE OF INFECTION ON  
ENDOMETRIAL GRAFTS.

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The Influence of Infection on Endometrial Grafts

Ever since the publication of Von Franque's book on Salpingitis Isthmica Nodosa the theory of an infective cause for adenomyomata has had many supporters. It seemed therefore a possible line for further experimental work, and it was decided to perform some experiments in order to observe the effect of infection on the growth of these endometrial implants. Two lines of investigation presented themselves. If infection was a factor, was adenomyomatous growth the result of a chronic infective process or was it necessary for infection to be present merely at the time of endometrial dissemination. To investigate the former possibility it was decided to produce first of all a chronic infection in the genital tract of female rabbits and at a later date to transplant the endometrium of these animals as in the previous experiments. To test the second possibility it was decided to infect the grafts and the site of implantation at one experiment and to observe the result.

For the first series of experiments four different cultures of organisms were employed, namely, *Bacillus Coli*, *Staphylococci*, *Streptococci* and a



culture containing a mixture of all three organisms. Using a fine blunt syringe an emulsion of each was injected into four rabbits, the syringe being passed through the vagina into each uterine cornu, and to assist this procedure laparotomy was performed at the same time in order to make certain of the success of the injection. The animals were allowed to recover and thirty days later a second laparotomy was performed. In every case operation showed no trace of any infection having occurred either in the genital tract or in the pelvis and though the experiment was repeated several times it was found impossible to produce pelvic infection in rabbits in any way comparable to that found in the human female, though in a few of the cases where a streptococcal emulsion was injected the rabbits failed to survive more than a few days. However, it was thought that chronic infection might be present though not apparent, so at the second operation endometrial transplants were performed in the routine way. At the same time a specimen of the uterine wall was removed and examined microscopically for evidence of infection, but none was found, the microscopic appearance being perfectly normal. The animals were killed thirty days later and in all cases the grafts were found to have persisted and to

have embedded themselves in the usual way.

Microscopic examination of these implants showed them to be exactly the same as in the previous experiments. The experiments cannot be said to have proved anything owing to the impossibility of producing chronic pelvic infection in rabbits, and as the sections showed nothing new it was not thought necessary to include them.

In the second series of experiments similar emulsions of organisms were used. In three cases the ordinary routine transplantation operations were performed but the grafts and the area in which they were embedded were smeared with the respective cultures at the time of grafting. Thirty days later the animals were killed and the grafts examined. In all cases where the rabbits survived the grafts had taken and the macroscopic appearances were similar to those seen in the routine cases. Again, microscopic examination showed no evidence of infection and showed the grafts to be exactly similar to those produced in the early experiments. In view of this, and in view of the additional photographic work involved, it was not thought that any useful purpose would be served by including them. Again, nothing has been proved by these experiments owing to the difficulty, one might say the apparent impossibility, of infecting rabbit tissues with ordinary organisms.



THE EXPERIMENTAL PRODUCTION OF  
ENDOMETRIOSIS.

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In many of the previous experiments it has been a very noticeable fact that those endometrial grafts placed in or near to the ovaries have shown the most persistent and vigorous growth suggesting the possibility of some peculiar attraction or affinity between ectopic endometrium and ovarian tissue. An experiment was conceived to test the possibility of the existence of such an affinity. In the experiment an endometrial graft was inserted into an ovary in the same animal and the ovary plus the graft was then buried in the abdominal wall. A second endometrial graft of approximately the same size was then placed in the abdominal wall in close proximity to the ovary in order that growth in the two grafts might be compared.



EXPERIMENT NO. XVIII.

A large fully grown female Angora rabbit was used. On opening the abdominal cavity the viscera were seen to be healthy and the pelvic organs were in the quiescent state. Using the same technique as before the left uterine cornu was resected and the endometrium shaved off. The right ovary was then excised and an endometrial graft was inserted in a stab wound in its substance and retained there by a catgut ligature. The peritoneum was closed and the ovary with the graft in it was embedded in the rectus muscle to the right of the lower end of the incision. About one inch distance from it an endometrial graft was buried in the rectus muscle in the routine way as a control. The abdominal wall was then closed.

Sixty days later the rabbit was killed and examined post mortem.

Post mortem Examination.

On reflecting the skin the two grafts in the abdominal wall were easily seen projecting under the aponeurosis covering the recti muscles (Fig. 74 A. & B.). The ovary was if anything slightly longer than when inserted but on close examination no sign of the endometrial graft which had been buried in it

Macroscopic appearance of grafts in  
abdominal wall.

FIG. LXXIV.

OVARY CONTAINING  
ENDOMETRIAL GRAFT  
IN ABDOMINAL WALL (d)



SIMPLE ENDOMETRIAL  
GRAFT IN ABDOMINAL WALL. (b)

THE ABOVE PHOTOGRAPH TAKEN POST MORTEM AFTER  
REFLECTION OF THE SKIN SHOWS THE APONEUROSIS  
OVER THE RECTI MUSCLES. AT THE LOWER END (a and b)  
THE GRAFTED OVARY AND THE SIMPLE ENDOMETRIAL  
GRAFT CAN BE SEEN.



could be seen. About half an inch distant was a small thin walled cyst in the site where the control graft had been inserted and similar in all respects to those cysts obtained in previous experiments. Both specimens were removed carefully for microscopic examination.

Microscopic Examination.

Fig.LXXV. Endometrial cyst in abdominal wall.



Above we see the control graft which has formed a bilocular cyst exactly similar to those obtained in other experiments. It is growing between two muscle layers which have separated to enclose it, but there is no infiltration of adjoining tissue by the endometrium.

FIG. LXXVI.

High Power.

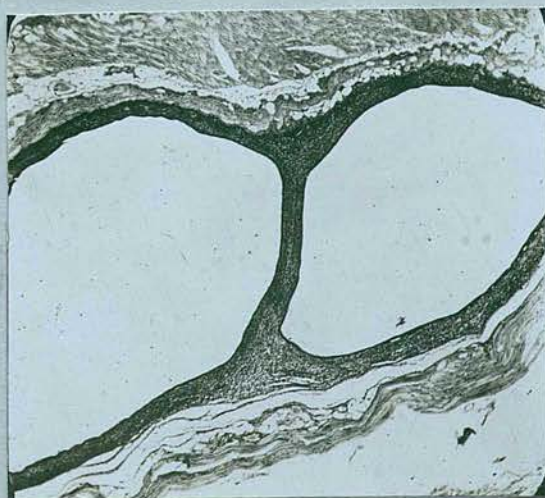
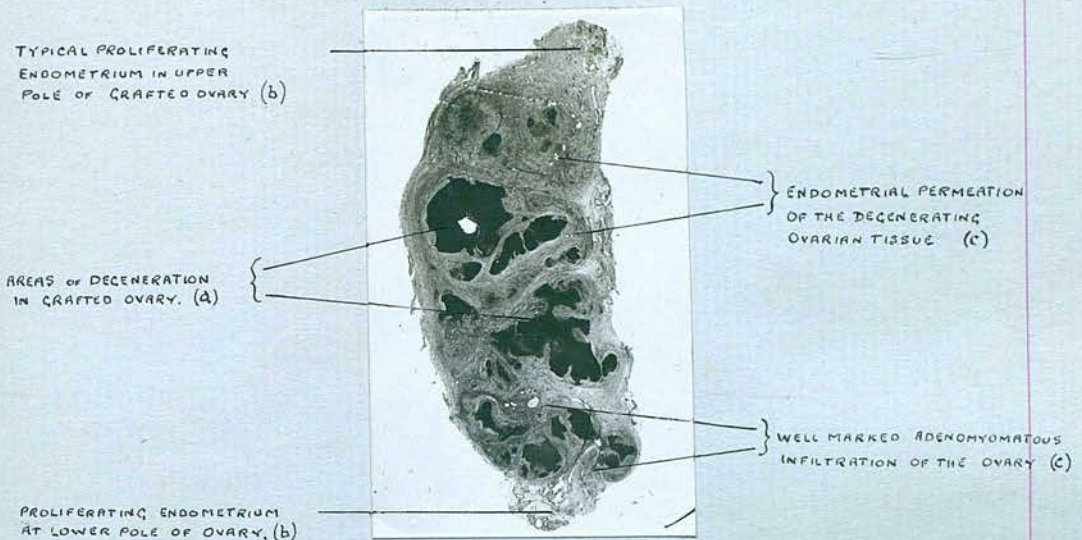




FIG. LXXVII. Grafted ovary with endometrial graft incorporated.

Low Power.



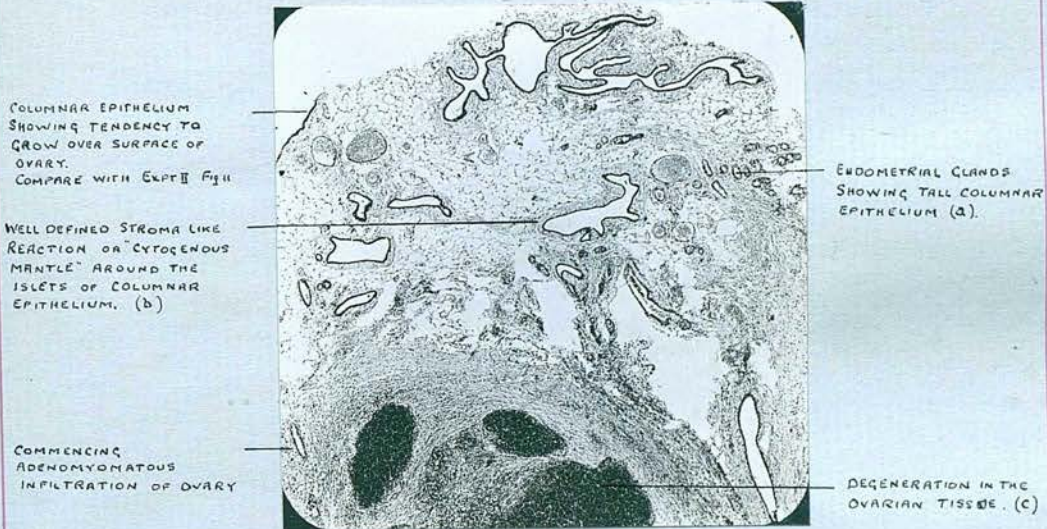
Microscopic examination of the grafted ovary in which an endometrial graft had been inserted revealed a remarkable and totally unexpected condition. Here we see the typical infiltrative type of endometrioma throughout a large part of the substance of the ovary. In the ovary are many areas of degeneration (Fig. 77-A.), doubtless consequent upon its transference to the abdominal wall and a resultant diminished blood supply, but a considerable amount of ovarian tissue still survives. The surviving portion shows some degenerative changes, there being a loss of cell definition and a tendency to diffuse hyaline degeneration. At both poles of the



ovary and infiltrating a large portion of the ovarian tissue islets of endometrium can be seen (Fig. 77- b.) which tends to invade those portions of the ovary lying between the areas of degeneration (Fig. 77- c.).

High Power.

Fig. LXXVIII. Endometrial graft  
in grafted ovary



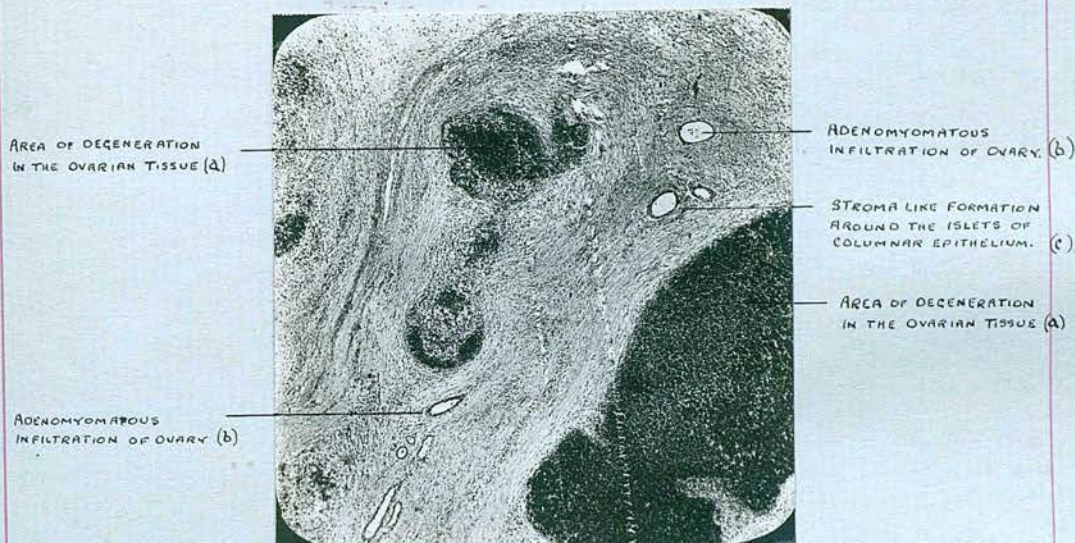
This microphotograph shows a large area of endometrium at one pole of the ovary. The columnar epithelium is well defined but tends to be of the cuboidal type as though growing rapidly, though in some of the small gland tubules it has the normal tall columnar appearance (Fig. 78- a.). Around the islets of epithelium there is a stroma like reaction in the adjacent connective tissue (Fig. 78- b.). In the lower part of the section there are some areas of degenerated ovarian tissue and possibly lutein



tissue, (Fig. 78- c.) and at either side islets of columnar epithelium can be seen commencing to infiltrate the ovary proper.

High Power.

Fig. LXXIX. Endometrial graft in grafted ovary.



This microphotograph, taken from the centre of the ovary, shows very distinctly the infiltration of the ovarian substance by the columnar epithelium and shows a picture almost identical with that of ovarian endometriomata as seen in the human female. Two areas of degeneration (Fig. 79- a.) can be seen and between them there is a stream of infiltrating columnar epithelium (Fig. 79- b.). This infiltration is taking place along the line of the connective tissue septae, and around the islets of epithelium there is an attempt



on the part of the connective tissue to undergo a stroma like reaction with the formation of a "cytogenous mantle". (Fig. 79 - c.).

The result obtained in this Experiment is of very great interest and possibly of some importance. For the first time and after many and varied experiments a fairly accurate type of true diffuse infiltrating endometriosis has been produced, perhaps somewhat unexpectedly. It has been produced, not in a normal ovary but in one that had been grafted into the abdominal wall together with the embedded endometrium.

Consideration of the factors governing this experiment reveals a new factor and one which has not featured in any of the previous experiments, namely, the invaded medium was not normal tissue. The ovary having been transplanted from the normal site must have become, to some extent, devitalised and it is conceivable that in a devitalised state it became more liable to a widespread invasion by the implanted endometrium. Even if this explanation is incorrect the result obtained is of sufficient importance to call for confirmation. It was decided to repeat the experiment and in doing so to use as far as possible the same method and technique.

Six further experiments were performed, the same technique being adopted as in Experiment XVIII but in all of these owing to various circumstances no positive results were obtained. In four cases the animals died or had to be destroyed on account of epidemic diarrhoea, in one case the grafts disappeared and no trace could be found post mortem, and in the remaining case the abdominal wound did not heal and the grafts could not be identified in the wide area of granulation tissue.



EXPERIMENT NO. XIX.

A fully grown Angora rabbit was used for the experiment. The same technique was employed as in Experiment XVIII, the right ovary and left uterine cornu being resected, the endometrium from the latter being shaved off and a portion embedded in a stab wound in the ovary by fine catgut ligatures. The ovary with the implanted graft was then fixed in the abdominal wall at the lower end of the incision and a control graft of endometrium only was similarly grafted some distance away at the upper end of the wound. Sixty days later the rabbit was killed and a post mortem examination was made.

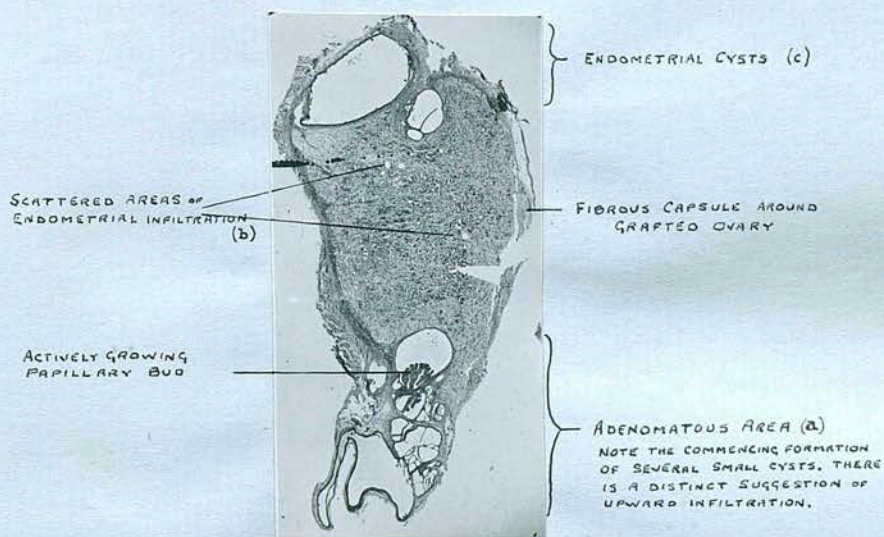
Post Mortem Examination.

On reflecting the skin both grafts could be identified readily. At the lower end of the wound the ovary appeared as a whitish yellow looking nodule, rather smaller than when inserted, and loosely bound to the adjoining rectus sheath by fine adhesions. The point where the graft had been embedded could be recognised by the retaining ligatures which had not completely dissolved, but the graft itself could not be discovered. At the upper end of the wound the isolated endometrial graft had formed a small thin walled multilocular cyst

similar to those produced by simple endometrial grafts in all the earlier experiments. The ovary with the embedded graft was removed, fixed and embedded and was then cut by serial sections.

Microscopic appearances.

Fig.LXXX. Grafted ovary with endometrial graft incorporated.



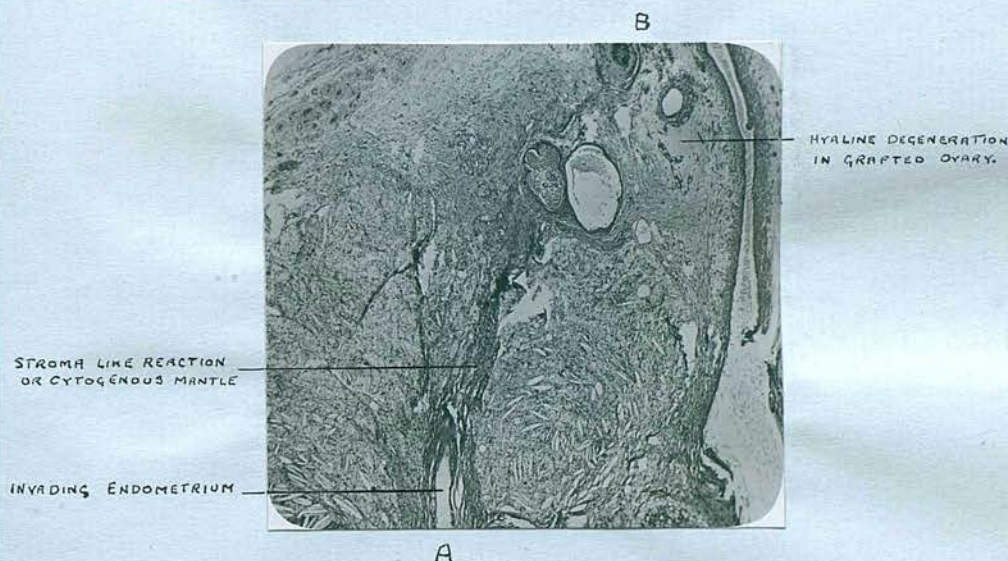
The microscopic appearances are somewhat similar to those in Experiment No. XVIII. Again there is an appearance suggestive of diffuse infiltrative endometriosis with islets of endometrium permeating the ovarian substance. At the lower pole is an area occupied by large and small cystic spaces lined by columnar epithelium, one of which (a) contains actively growing papillary buds. The ovarian tissue shows some hyaline and granular change but scattered throughout can be seen a few small



epithelial islets (b), while at the upper pole is a large cystic space lined by columnar epithelium (c) with a smaller area of endometrial infiltration deeper in the ovary. The appearance of diffuse infiltrative endometriosis is not so typical as in the previous experiment but there is a degree of infiltration not found in the ordinary simple grafts.

FIG. LXXXI. Endometrial graft in grafted ovary.

High Power.

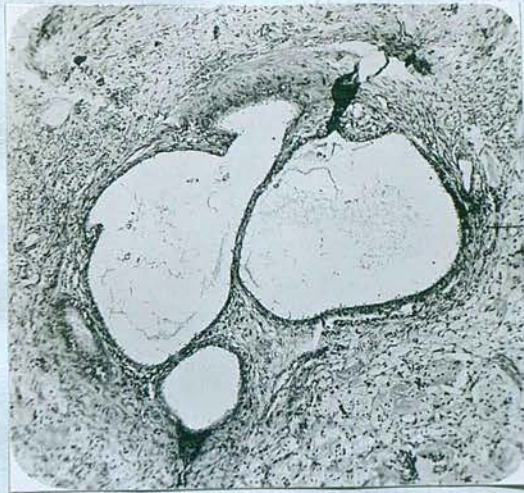


Under high power the infiltrative process is more apparent. From A to B a line of endometrial permeation can be seen, showing gland spaces lined by columnar epithelium and surrounded by a thin layer of stroma invading the ovary. The ovarian tissue shows some areas of hyaline degeneration though fairly normal ovary still remains.



FIG. LXXXII. Endometrial graft in grafted ovary.

High Power.



ABOVE IS SHOWN A SMALL ENDOMETRIAL ISLET IN THE GRAFTED OVARY WITH LARGE AND SMALL GLAND SPACES. THERE IS A WELL DEFINED REACTION IN THE ADJOINING OVARIAN TISSUE GIVING THE APPEARANCE OF STROMA. THE APPEARANCE IS ALSO THAT OF ACTIVE PERMEATION.

Higher magnification shows an epithelial islet with several small gland spaces lined by low cuboidal epithelium. Surrounding these gland spaces is a distinct stroma like reaction in the invaded ovarian tissue which in one area still preserves the appearance of normal ovary.



EXPERIMENT NO. XX.

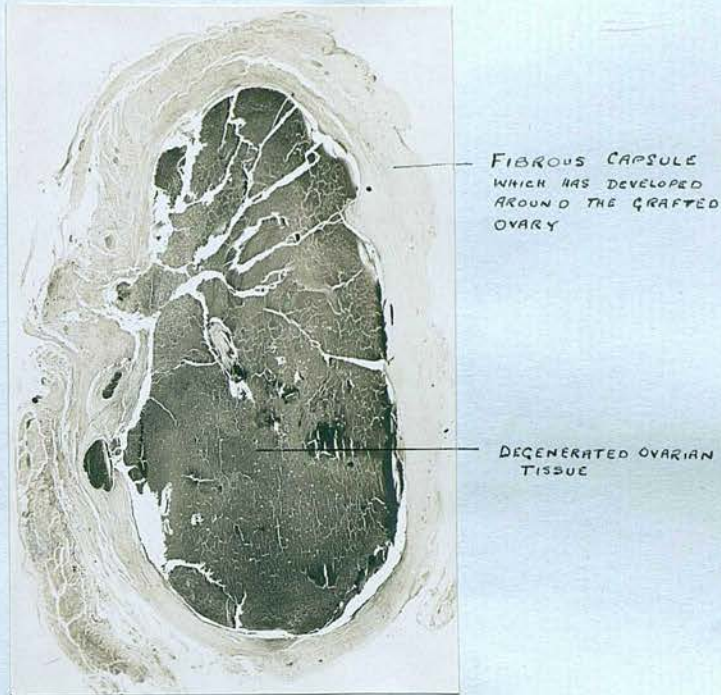
A fully grown female rabbit was employed and the technique adopted in Experiment was followed carefully. The right ovary was resected together with the left uterine cornu and the endometrium from the latter was stripped off and buried in a stab wound in the ovary. The ovary with the embedded graft was buried in the rectus muscle of the abdominal wall and a simple endometrial graft was embedded similarly at some little distance. Forty two days later the rabbit died of epidemic diarrhoea and was examined post mortem.

Post Mortem Examination.

The two grafts were easily located, the ovary forming a solid nodule firmly adherent to the muscle and the loose endometrial graft forming a small cystic swelling somewhat similar to those seen in many previous experiments. The ovary and the control graft were removed for microscopic examination.

Microscopic Examination.

Fig. LXXXIII. Ovary with endometrial graft in abdominal wall.



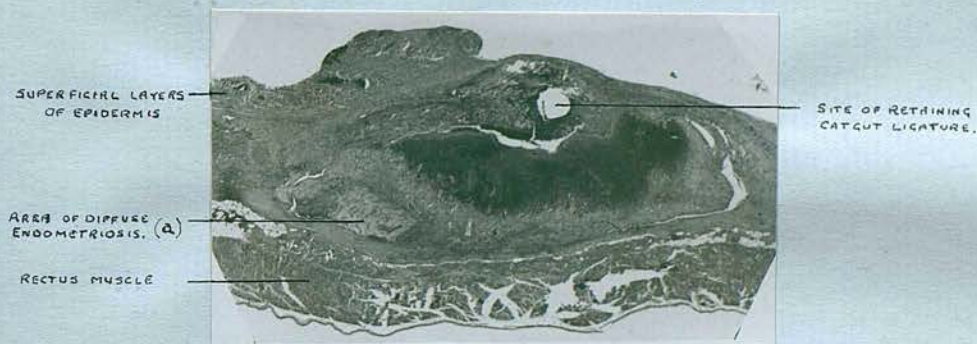
Seen in sections the ovary shows an appearance quite unlike that in the previous experiment. It is encysted completely in the rectus muscle and has degenerated to such an extent that normal ovarian tissue can no longer be identified. No endometrium can be found and it appears that both ovary and graft for some inexplicable reason have failed to survive.



When the control graft was examined, however, it was surprising to find the typical appearance of diffuse infiltrative endometriosis. One had expected to find this in the ovarian graft, as in the previous experiments, but for some not too apparent reason this mode of growth had developed in the simple graft.

Microscopic appearance.

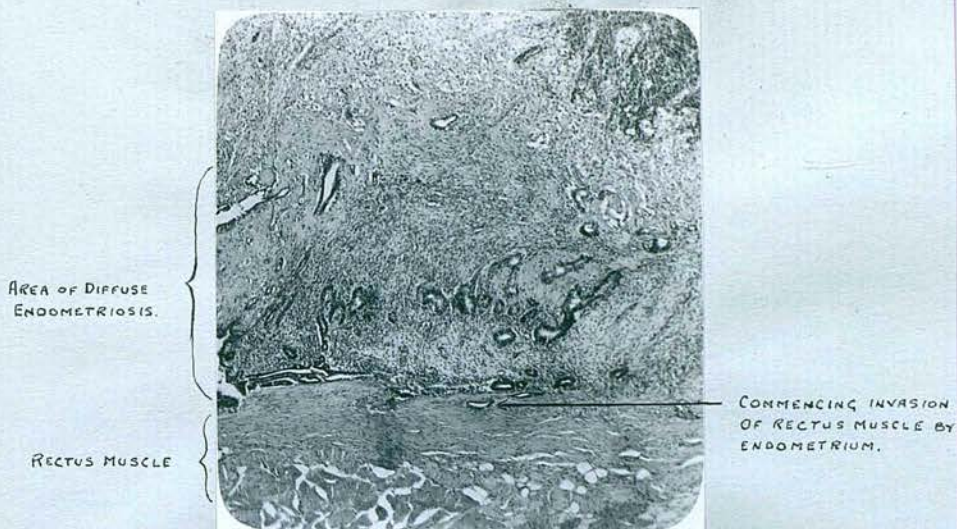
Fig. LXXXIV. Endometrial control graft  
in abdominal wall



The microphotograph shows rather imperfectly portions of the abdominal wall with the endometrial graft. At (a) is a small area of endometrium forming an adenomyomatous nodule throughout which are scattered islets of columnar epithelium. Below this is the rectus muscle and superficial to it the epidermis.



Fig. LXXXV. High Power.



Under higher magnification the typical appearance of diffuse endometriosis is at once apparent. Scattered throughout the sub epidermal connective tissue are numerous gland acini lined by columnar epithelium and enveloped by a thin layer of stroma. In the lower part of the field commencing infiltration of the muscular layer can be seen, but there is a complete absence of any suggestion of cyst formation which has so constantly been found in the case of all simple grafts.

The reason why it has been possible to produce fairly typical endometriomata in these three experiments can only be surmised. I thought after the two experiments where the ovary itself with the embedded endometrium was transferred to the



abdominal wall and where diffuse endometriosis resulted, that the cause was to be found in the devitalisation of the ovary. The assumption that the endometrium could become invasive in a devitalised medium when it could not do so in normal healthy tissue seemed not unreasonable, but in Experiment XX endometriosis has occurred with a simple graft in the abdominal wall. Moreover, this experiment shows that "endometriosis" in the abdominal wall could not originate from epithelial tissue in the grafted ovary, a suggestion that otherwise could not have been overlooked. I think that in these three experiments several factors acting together have been responsible for the positive results. We have seen that ectopic endometrium in vascular sites such as the liver and normal ovary grows rapidly and that the islets of columnar epithelium tend to become confluent with the result that cyst formation ensues. Intracystic pressure from the retained secretion of the epithelium then tends to cause a degree of pressure atrophy on the lining epithelium so that growth ceases and gradual atrophy sets in. In all probability, for the production of diffuse infiltrative endometriosis, the progress and growth of the aberrant endometrium must be slow and

difficult. If growth is slow it retains its acinar formation and cyst production does not occur. In these three experiments we find factors favourable for this mode of growth. In the first two transference of the ovary cut off its blood supply so that the grafted endometrium probably only survived with difficulty and so retained its normal acinar formation. In Experiment XX it is possible that during insertion of the graft the blood supply to the area of implantation was damaged. It is also not improbable that an associated devitalisation of the tissues in the immediate vicinity of the aberrant endometrium allows the invasive process to commence, though when once established this infiltration may extend into the normal healthy tissues. Again, muscular and connective tissue such as is present in the abdominal wall, is a specially suitable field for such a slow infiltrative process. It is not too vascular, thus preventing rapid cyst formation and is made up in fascial planes and muscle bundles and it is the small spaces between these planes and between these muscle bundles that are favourable for a process of permeation.

We find many similar features in endometriosis in the human female. The slow infiltrative type



of endometrial permeation seen in the Uterus resembles that seen in these experiments, the relative avascularity of the Uterus and its formation interlacing muscular bundles being favourable to a slow infiltrative process. Also endometriomata of the abdominal wall following operation may be explained on the result of these experiments. The mere accidental implantation of endometrium in the abdominal wall may not be sufficient to start an endometrioma, but if at the same time the tissues in the vicinity of the scar are devitalised by trauma or say ligatures that are too tight, then conditions may be made favourable for the commencement of abnormal growth. We see further similarity between these animal tumours and "tarry ovarian cysts". When in the human female the aberrant endometrium reaches the ovary, its vascularity is favourable for rapid growth and so cyst formation results. The endometrium in these tarry cysts is soon reduced to a layer of low cuboidal epithelium by intra cystic tension and so, though one can usually find typical endometrial like tissue in small early tarry cysts it is almost impossible to define it in the more mature. It is this pressure atrophy of the lining columnar epithelium that accounts for the comparative small size of even the largest of tarry ovarian cysts.

C O N C L U S I O N S

1. Transplanted endometrium in rabbits will, in practically all cases, continue to live in the new site, such growth continuing throughout the lifetime of the animal.
2. Following transplantation the grafts go through the following phases: Firstly, a period of degeneration, secondly, a process of repair, then a phase of renewed growth, and lastly, and almost invariably, a proliferative phase ending in cyst formation.
3. That the mode and rapidity of growth is dependent on the site of implantation. In vascular sites growth is more rapid, the normal acinar structure of the graft is soon lost and cyst formation occurs early with resulting pressure atrophy on the cyst wall. In avascular sites growth is slower and the normal acinar formation of the endometrium tends to be preserved for a longer period, though cyst formation is the invariable end result.



4. That the columnar epithelium will leave the stroma of the graft and spread rapidly over all adjoining surfaces much in the same way that a drop of oil will spread over a relatively large surface of water. In the case of peritoneal surfaces it would appear to spread by displacing the serosal epithelium. The stroma in such dissemination does not accompany the epithelium but the latter provokes a "stroma like" reaction in the subjacent connective tissue.
5. That increase in the corpus luteum hormone causes marked increase in the rate of growth of these endometrial grafts.
6. Deprivation of the ovarian hormones causes atrophy of the grafts. It would appear that the columnar epithelium is much more sensitive to the hormone influences than the stroma.
7. In rabbits infection does not appear to have any influence on the behaviour of endometrial transplants.

8. No confirmation of the "serosal theory" for the origin of adenomyomata is obtainable by animal experiments. The contrary would appear to be the case, for these experiments show that it is impossible for the serosal epithelium to survive when buried beneath the surface.
9. There is some evidence to show that devitalisation of the tissues at the site of implantation of endometrial transplants is an important factor in the production of true diffuse infiltrative endometriosis.



THE APPLICATION OF THESE EXPERIMENTAL  
FINDINGS TO THE PROBLEM OF THE ETIOLOGY  
AND MODE OF GROWTH OF ENDOMETRIOMATA  
IN THE HUMAN FEMALE.

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The clinical aspect of endometriomata as occurring in the human female with a study of illustrative cases is scarcely within the scope of this thesis. I think, however, that some of the findings in this experimental work might be of help in formulating a hypothesis as to the mode of spread of the epithelial tissue in adenomyomata. For this reason I would like to describe one single case which, though atypical in some aspects of the history shows a fairly typical pathological picture, and demonstrates the analogy between some of the experimental findings and a possible mode of spread of the epithelial elements in this particular case.

The history of the case was as follows:-

Mrs. A. Aged 40.

Fifteen years ago - one year after the birth of her only child - she was admitted to hospital in Capetown on account of pelvic peritonitis for which laparotomy and drainage was performed. A gonorrhoeal infection was suspected and patient had reason to believe she had acquired this from her husband. After recovering she returned to this country and shortly afterwards developed acute arthritis of the right hip joint which resulted in partial ankylosis. A metastatic gonorrhoeal infection was considered to be



the cause and excision of the head of the femur became necessary.

After the first operation she developed a dull aching pain in the sacral region eased by the decubitus and aggravated before and during menstruation. There was also some moderate pre-menstrual dysmenorrhoea, some irregularity of the menstrual periods though no menorrhagia, and a chronic yellow discharge. These symptoms persisted with little variation during the next fourteen years, though the sacral pain tended to become gradually worse.

Three months before I saw her the symptoms suddenly became more acute. The sacral pain became much more intense and she developed some tenesmus and severe pain on defaecation. The pre-menstrual and menstrual dysmenorrhoea became more acute and had increased in intensity with each of the three previous menstrual periods, and during these three periods the loss had increased in amount and the duration had lengthened from five to ten days. There was no history of dyspareunia as she had been separated from her husband for many years.

Previous Medical History: Apart from the ill health resulting from the pelvic peritonitis she had never had any severe illness.

Condition on Examination: Patient was

moderately well nourished but looked anaemic and ill, and had the appearance of being considerably older than her years. Abdominal examination revealed a scar in the mid line below the umbilicus with a puckered cicatrix at the lower end, apparently resulting from a drainage tube. There was a feeling of resistance in the mid line above the pubes and low down in both iliac fossae and there was marked tenderness on deep pressure in these areas. Examination of her back revealed some compensatory scoliosis but no tenderness on pressure was obtainable.

On vaginal examination the Vulva and vaginal wall were found to be healthy and well supported. The Cervix was somewhat hypertrophied and speculum examination showed a deep tear in the left side with ectropion of the cervical mucosa. The body of the Uterus was somewhat enlarged, retroverted and fixed and some hard, fixed and very tender nodules were palpable in the posterior fornix. On rectal examination an irregular swelling could be felt above the Cervix and bulging into the rectum and which was extremely tender on pressure.

The diagnosis lay between diffuse pelvic endometriosis and chronic bilateral salpingo oophoritis, and operation was advised.



Operation: The abdomen was opened by a left paramesial incision below the umbilicus. The omentum was found to be adherent to the old scar and to the left appendages and was separated and freed. On exploring the pelvic viscera the Uterus was seen to be almost double the normal size and to be retroverted. The tubes could only be distinguished with difficulty and on either side behind the Uterus was a dark coloured, thick walled cystic swelling - both of which were densely adherent to the posterior aspect of the Uterus and broad ligaments in front and to the rectum and postero lateral pelvic walls behind. On attempting to dissect out these "ovarian cysts" they ruptured and discharged a large quantity of dark chocolate coloured fluid. The case was seen to be one of diffuse endometriosis and hysterectomy was decided upon. Both cysts were freed but very considerable difficulty was experienced in separating the posterior surface of the Uterus from the anterior rectal wall, the Pouch of Douglas being obliterated by dense fibrous tissue which in parts was almost an inch thick. After separation of these adhesions pan hysterectomy was performed, which was followed by an uninterrupted recovery.

FIG. LXXXVI

Specimen of Uterus, Cervix and Appendages

from Case of diffuse pelvic

endometriosis.

-----

C

B

D

A

- A. Large Chocolate Cyst R. Ovary
- B. Small Chocolate Cyst L. Ovary
- C. Diffuse adenomyoma of posterior  
uterine wall
- D. Rough area on posterior surface  
of uterus after separation  
from rectum.





SPECIMEN.

This consists of the Uterus and Cervix, both appendages and a certain amount of fibrous tissue from the recto vaginal septum.

The Uterus was appreciably enlarged, the length from fundus to Cervix being  $4\frac{1}{4}$ ", the posterior surface being rough and shaggy when it had been separated from the rectum. The walls were all thickened and appeared hard and fibrous, but this thickening was most marked in the posterior wall which was between 1" and  $1\frac{1}{2}$ " in thickness. Scattered just below the peritoneal surface of the posterior wall were numerous small, almost black, areas typical of diffuse endometriosis of the uterine wall.

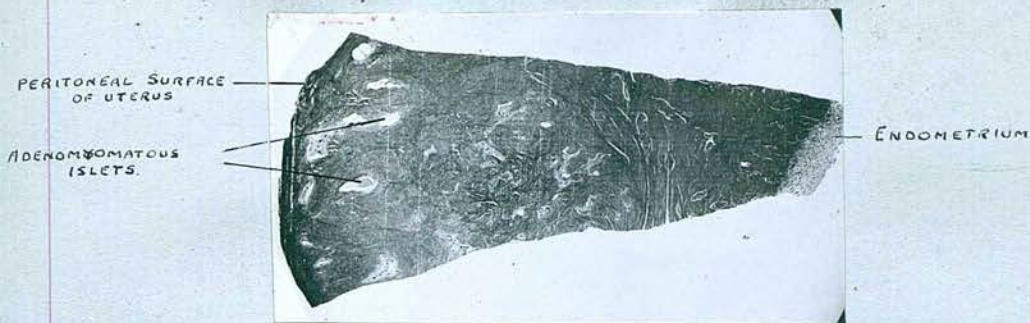
The right ovary was considerably enlarged and was replaced by a "tarry cyst" from which a large quantity of dark chocolate coloured fluid had escaped through a hole in the posterior surface where it had been separated from the posterior uterine wall. The walls of the cyst varied in thickness from  $\frac{1}{8}$ " -  $\frac{1}{4}$ " and no typical ovarian tissue could be distinguished. The right tube was adherent over the anterior surface of the cyst, was hard, nodular and thickened, and no fimbriated end could be recognised.



The left ovary was rather smaller and also had become converted into a cyst containing chocolate coloured fluid and which had also escaped during dissection. A thin layer of ovarian tissue was recognisable in the anterior wall. The left tube was adherent over the cyst and also was hard, nodular and thickened and neither the fimbrae nor the abdominal ostium were recognisable.

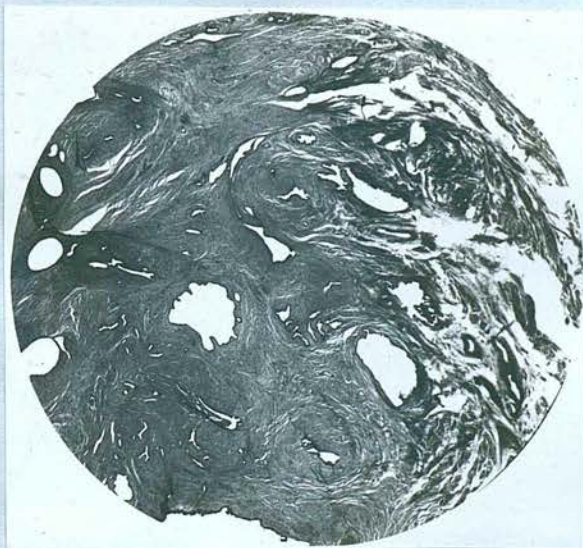
Microscopic Examination.

FIG. LXXXVII. Section from Right Uterine Cornu.



The section is taken through the whole thickness of the uterine wall in the region of the right cornu and shows typical salpingitis isthmici nodosa with islets of endometrium scattered throughout the outer two-thirds.

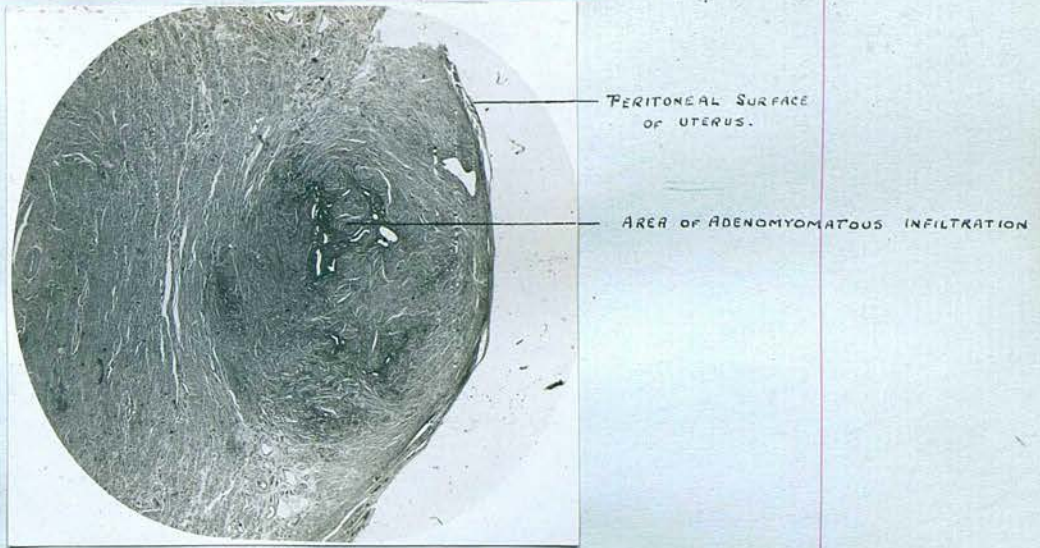
Fig. LXXXVIII. High Power.



THIS SECTION SHOWS MANY SMALL CYSTIC SPACES LINED BY COLUMNAR EPITHELIUM SCATTERED THROUGHOUT THE MUSCULATURE OF THE UTERINE WALL IN THE REGION OF THE CORNU. THERE IS WELL DEFINED PERMEATION OF THE INTER MUSCULAR PLANES, BY THE GLANDULAR ELEMENTS.

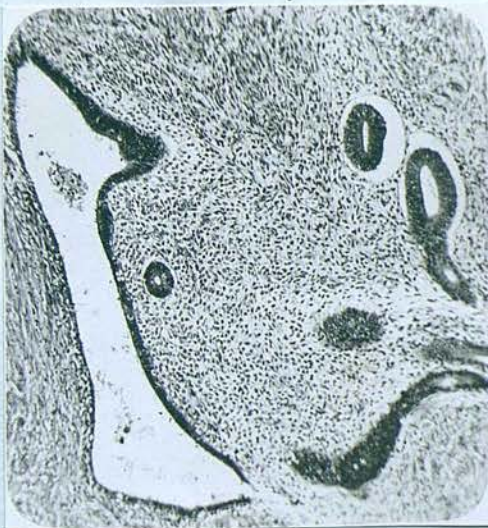


Fig. LXXXIX. Posterior Uterine Wall



This section taken through the posterior uterine wall shows an area of diffuse adenomyoma just below the peritoneal surface with scattered glandular elements surrounded by stroma.

Fig. XC. High Power



THE SECTION SHOWS GLANDULAR ELEMENTS OF ENDOMETRIAL TYPE. THE SMALL TUBULES ARE LINED BY TALL COLUMNAR EPITHELIUM BUT IN THE LARGER GLANDULAR SPACE THE LINING EPITHELIUM VARIES FROM TALL COLUMNAR TO LOW CUBOIDAL EPITHELIUM. SURROUNDING THE GLAND ELEMENTS IS A WELL DEFINED CYTOGENOUS MANTLE.



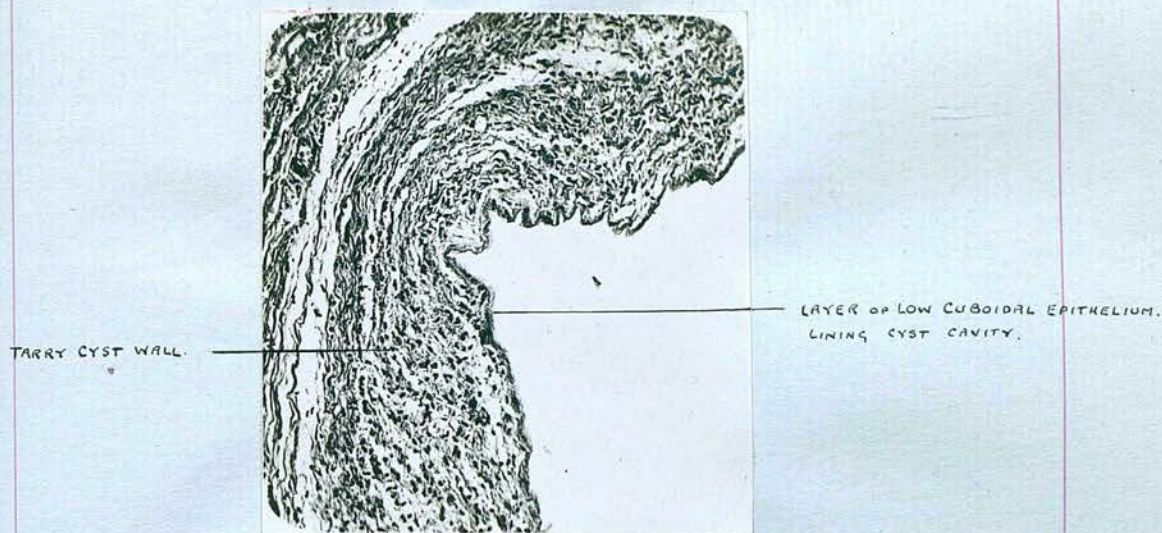
Fig. XCI. Left Ovary



This section taken through portions of the wall of the left tarry cyst shows an area of endometrial like tissue with glandular acini lined by tall columnar epithelium and surrounded by connective tissue cells indistinguishable from a normal stroma. The left ovary contained a small early chocolate cyst which presumably had not attained a large enough size for pressure atrophy to destroy the typical appearance of the endometrium. Similarly in all the animal experiments typical endometrium was only found in the walls of early cysts.



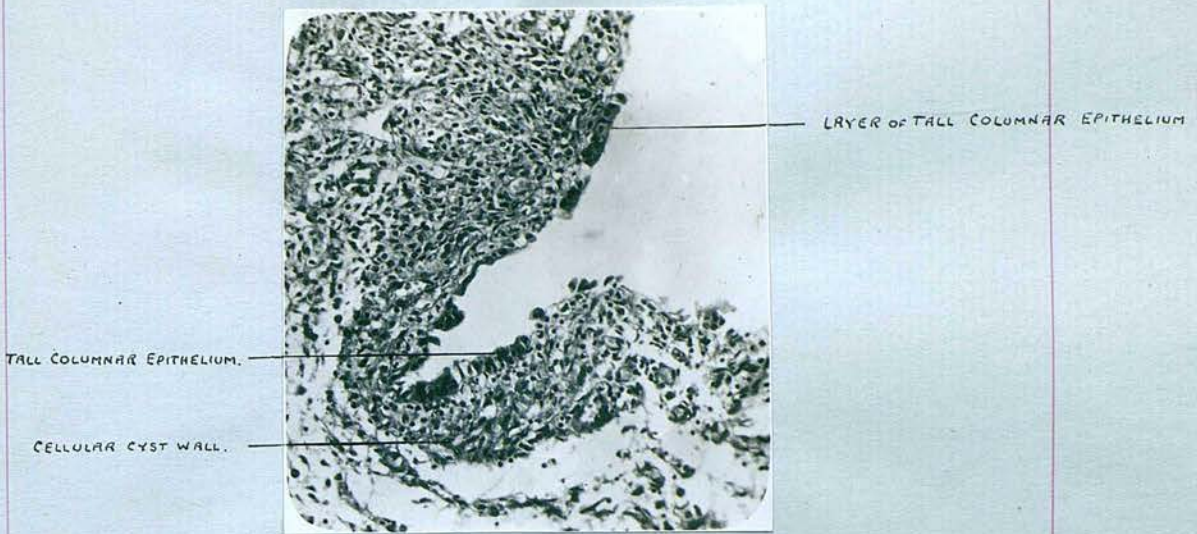
Fig. XCII.      Right Ovary



Here we see the cyst wall of the larger "chocolate" cyst. The endometrium has been reduced to a single layer of low cuboidal epithelium lining the cyst wall, and the wall itself is becoming fibrous. Presumably this is the result of pressure atrophy similar to that seen in many of the animal experiments.



Fig. XCIII. High Power



This shows a small area in the cyst wall still lined by tall columnar epithelium and preserving the appearance of endometrium. The subjacent layers are more cellular and pressure atrophy is less apparent.



This case presents many interesting features not usually found in diffuse endometriosis and which make an explanation by Sampson's theory somewhat difficult of acceptance. Firstly, there is a very definite history of an old ascending pelvic infection which is uncommon, and with this there are all the signs of chronic tubal inflammation and it is practically certain that occlusion of the tubal lumina must have been present for many years. Also there are two definite phases distinguishable in the clinical history, a long chronic phase extending over many years with moderate sacral pain, dysmenorrhoea and slight menstrual irregularity, followed by a short and acute phase, lasting a few months, of intense backache, dysmenorrhoea, menorrhagia and rectal pain and irritation. The possibility of retrograde menstruation seems unlikely as both tubes had almost certainly been occluded for many years, so in this case some other mode of endometrial dissemination must be sought for. I would like to put forward the following suggestions, based partly on the observations made in the experimental work, to explain in part the mode of endometrial permeation in this particular case.

The commencement of the infiltrative process must be assumed. The long standing infection must

have produced in the uterine wall some degree of fibrosis or true chronic metritis of the type (33 & 34) described by Fletcher Shaw and others. While, as is well known, a chronic infection will devitalise the mesoblastic tissues so will it tend to stimulate the covering epithelium, a process well known in such chronic infections as tubercle and syphilis, so that in the Uterus the nett result will be an active endometrium on a subjacent devitalised myometrium. From Experiment XVIII we have the suggestion that devitalisation of the adjacent tissues is a factor in allowing the infiltrative process to commence, so applied to this case we find, not only a devitalised myometrium, but an activated and stimulated endometrium that is, two factors both favourable for the onset of an infiltrative process like endometriosis. The association between tuberculosis of the Uterus and adenomyoma as described by Johnstone<sup>(45)</sup> may similarly be explained. I am inclined to agree with Leitch when he states that the starting point in such endometrial invasion is either the uterine cornu or the Cervix, the former because it is particularly exposed to inflammatory changes, and the latter because of its liability to trauma and infection. In my case I think the starting point of the endometrial invasion was probably in the



uterine cornua though the possibility of a cervical origin from the chronic cervicitis and cervical tear cannot be ruled out.

The permeation of the uterine wall must be a slow and prolonged process along the inter muscular spaces. That it is slow and difficult to trace even by serial sections is because there are longitudinal and circular muscle layers and even interlacing muscular bands so that wandering endometrium may progress in spiral fashion round and round the uterine wall before it invades the external longitudinal muscle fibres along which planes it can reach the peritoneal surface. I do not believe that the stroma accompanies these epithelial islets for it is a mesoblastic tissue and in no other form of tumour do we find mesoderm accompanying the epithelial invasion. In all the experiments, particularly Experiment II, we have seen that the columnar epithelium spreads over other tissues without any migration of stroma and that its presence provokes a stroma like reaction in the surrounding connective tissue. Thus we are justified in assuming that the epithelial islets manufacture their own stroma as they progress by stimulating the surrounding connective tissue, a process peculiar to the columnar epithelium lining the uterine cavity which

adds to the difficulty of the invasive process. Probably in many cases as the result of this arduous journey through the uterine wall, the endometrium never reaches the peritoneal surface but dies out before the outer surface is reached, and so the more widely disseminated type of pelvic endometriosis may not occur. Should, however, this columnar epithelium reach the peritoneal surface of the Uterus a new and more rapid phase of dissemination is entered upon. After the long and tedious journey through the resistant uterine wall the epithelium reaches an area rich both in blood and lymph and bathed in the lymph of the peritoneal cavity. Growth can, and now probably does, progress much more rapidly for our experiments have shown that the more vascular sites are most favourable for the growth of aberrant endometrium. Both these experiments and the culture of endometrium in artificial media have shown that the columnar epithelium spreads rapidly over a free surface, somewhat like a drop of oil on the surface of water, by a process of displacement of the serosal epithelium and that this occurs rapidly and in all directions. Thus the columnar epithelium spreads rapidly over the posterior surface of the Uterus and broad ligaments and so reaches the ovaries in which it commences another invasive



process. Consequently there may be, as in this case, two definite phases - a long chronic phase possibly extending over many years with only mild or moderate symptoms, followed by a much more acute and severe stage which signifies invasion of the ovaries and the formation of tarry ovarian cysts with multiple pelvic adhesions. Such a history is obtainable in many cases of diffuse pelvic endometriosis, and I think, provides some confirmation for this view.

There is one other feature in these cases of diffuse pelvic endometriosis not always adequately explained by Sampson's theory. Frequently we find, as in my case, a dense formation of fibrous tissue between rectum and uterus varying from a quarter to an inch in thickness. That such fibrous tissue is the result of an adenomyomatous invasion is proved by cases such as Fletcher Shaw's<sup>(32)</sup> where there was typical obliteration of the Pouch of Douglas by dense fibrous tissue resulting from an adenomyomatous invasion clearly shown to be originating from the cervical endometrium. In this case there was no ovarian involvement whatsoever. Such a thickness of fibrous tissue must take many years to form for the deposition of fibrous tissue is a slow process. In most cases of "tarry ovarian

cysts" there is a similar thickness of fibrous tissue obliterating the Pouch of Douglas which must have taken years to form, though the "acute phase" of the history shows the ovarian involvement to be comparatively recent. This suggests strongly the possibility in some cases of an ascending infiltration with secondary involvement of the ovaries, and not, as stated by Sampson, a downward dissemination with primary ovarian implantation.

One other point remains for discussion, namely, the reason for the very intense menstrual reaction found in endometriosis of the ovaries with the production of large quantities of menstrual blood as compared with the comparatively slight menstrual reaction provoked elsewhere by this aberrant endometrium.

For normal menstruation to occur in the uterine cavity three main elements are essential, namely, a layer of columnar epithelium, a bed of spongy vascular and cellular stroma and a periodic supply of ovarian hormone. These three elements are equally necessary for menstruation to occur in the aberrant endometrium of adenomyomata. Now in endometriomata the proportional amount of columnar epithelium and stroma vary enormously for we have



seen that the cytogenous mantle or acquired stroma around these wandering glandular islets is merely a response on the part of the invaded muscular or connective tissue to the presence of the columnar epithelium. In the cellular connective tissue of the uterine wall the creation of a certain amount of stroma is possible and so a modified menstrual reaction occurs. The formation of fibrous tissue in response to this invasion such as is found in the recto vaginal septum makes the manufacture of stroma a matter of difficulty, and so we find a much less marked menstrual reaction both in the recto vaginal septum and in the more fibrous outer portion of the Uterus, in fact the blood effusion in these sites is almost negligible. When, however, the columnar epithelium reaches the ovary the production of the necessary stroma is again possible. Here we have cells, particularly in the theca interna and theca externa closely akin to the normal stroma cells; they are embryonic in type, they multiply and disintegrate rapidly in response to the ovarian hormone, produce a periodic effusion of blood after dehiscence of the ovum and may even, according to de Jong, <sup>(26)</sup> and other observers undergo decidual reaction during pregnancy. Thus, once in the ovary, the wandering columnar epithelium can again manufacture a stroma

from these cells and so the profuse menstrual reaction that can produce the large quantities of menstrual blood found in "tarry cysts" is possible. With increase in size of the cysts there is a gradually increasing intra cystic pressure resulting in some degree of pressure atrophy such as we have seen in these Experiments and also in the actual cysts themselves. In the case I have recorded almost normal endometrium is seen in the smaller of the two tarry cysts and only a single layer of columnar epithelium in the large one, an observation that has been made by many workers. This tendency to pressure atrophy of the endometrium lining the cyst wall is the most probable reason for the comparative small size of all true endometrial cysts.



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